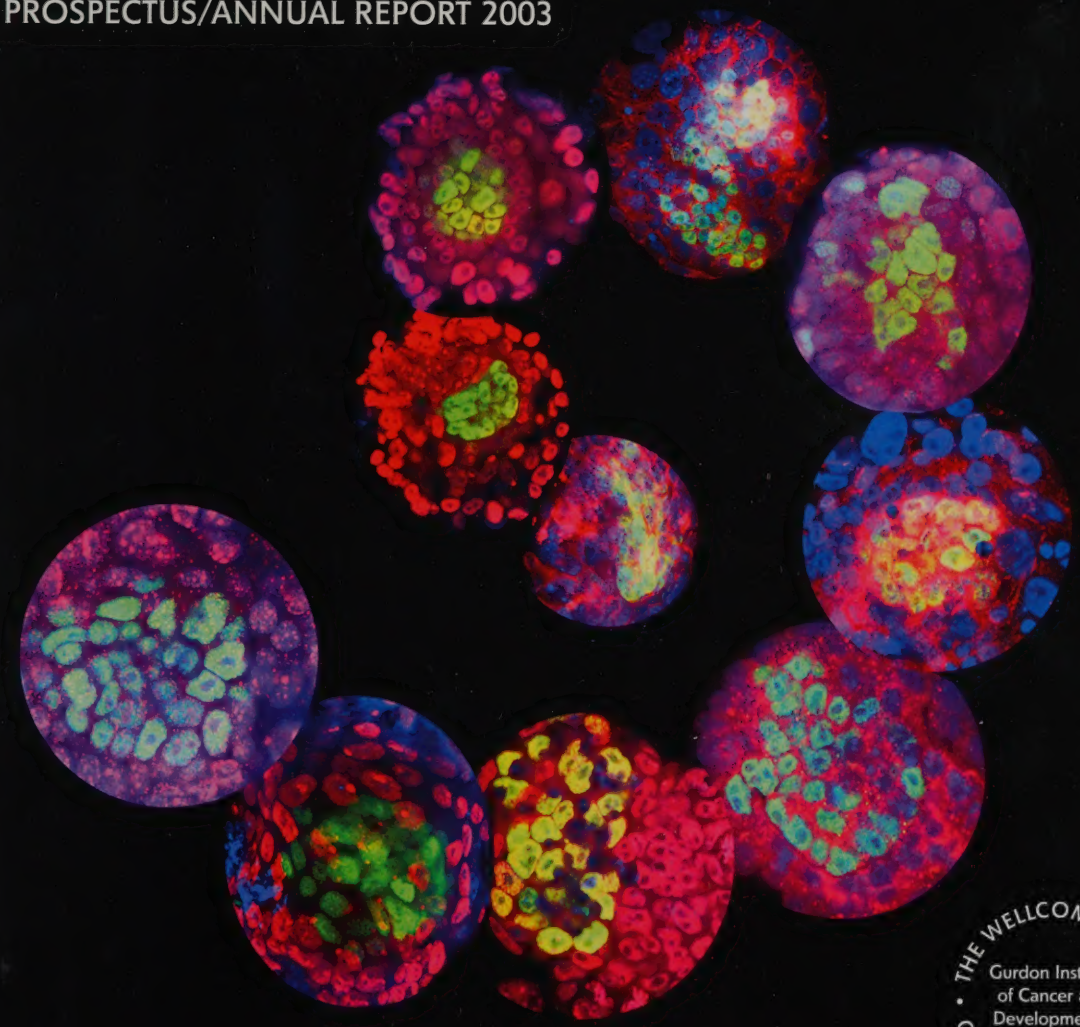
THE WELLCOME TRUST/ CANCER RESEARCH UK GURDON INSTITUTE

2004 PROSPECTUS/ANNUAL REPORT 2003



THE WELLCOME TRUST
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CHAIRMAN'S INTRODUCTION

In the course of 2004 the Institute will vacate the original Wellcome Trust/Cancer Research UK building, which we have occupied since 1991, and move into new accommodation. Our new building, funded by the Wellcome Trust and the Government's Office of Science and Technology, is just a hundred yards away along Tennis Court Road. The move will help relieve the overcrowding in the present building and will provide us with much improved laboratory space together with space for new equipment.

The other major change for 2004 is that the Institute is recognising one of its founders and longest-serving members by changing its name: we are now the Wellcome Trust/Cancer Research UK Gurdon Institute. With Ron Laskey and others, John Gurdon was one of the founding members of the Institute, and during his chairmanship he worked enormously hard to make the Institute the success it is today. While doing this he continued to carry out world-class research into developmental biology and nuclear reprogramming and we were delighted that in 2003 he was awarded the Copley Medal, the premier scientific award of the Royal Society. The Institute is honoured that John has allowed us to use his name, and we are delighted that he continues to carry out his research here.



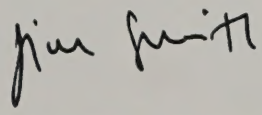
The heads of two nematode worms (*C.elegans*), one expressing the pharyngeal marker pha::GFP.

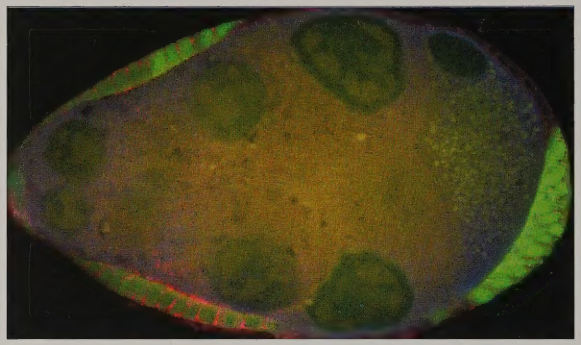
Other members of the Institute have also received international awards and recognition. These include Julie Ahringer, who was elected a member of EMBO; Andrea Brand, who was elected a Fellow of the Academy of Medical Sciences and is an Invited Professor at the Ecole Normale Superieure in Paris; and Steve Jackson, who received the Anthony Dipple Carcinogenesis Young Investigator's Award.

We have had a highly successful group of students, including Huw Williams, who was awarded the Poster Prize at the annual meeting of the Society for Developmental Biology in Boston.

Our group leaders receive funding from one or other of our major sponsors, the Wellcome Trust and Cancer Research UK. We are very pleased that Nick Brown was awarded a generous Programme Grant by the Wellcome Trust this year, and that Eric Miska will be joining us during 2004 as a Cancer Research UK-funded group leader.

Finally, the Institute's International Advisory Board visited in 2003, and, as usual, made some very helpful and constructive comments about our science and the way we run the Institute. Members of the IAB are listed at the back of this Prospectus. We are very grateful to them for giving up their valuable time to help us.





Stage 9 *Drosophila* egg chamber containing Notch follicle cell clones (Isabel Torres, 2003).

HISTORICAL BACKGROUND

The Institute will continue to be situated in the middle of the area containing the science departments of the University of Cambridge and within a short distance from the centre of the historic city. Founded in 1989 to promote research in the areas of developmental biology and cancer biology, the Institute is an assemblage of independent research groups located in one building designed to promote as much interaction as possible. Developmental and cancer biology are complementary since developmental biology is concerned with how cells acquire and maintain their normal function, whereas cancer is a result of a cell breaking loose from its correct controls and becoming abnormal. Both areas require a detailed knowledge of intercellular processes, which need to be analysed at the cellular and molecular levels. These research areas are complementary at the scientific and technical levels. To understand what goes wrong when a cell becomes cancerous requires knowledge of the processes that ensure correct function in normal development. At the technical level, the analysis of cellular and molecular processes requires familiarity with techniques that no single person can master, such as gene cloning, antibody preparation, cell culture, microarray technology, imaging and embryonic manipulation. There is, therefore, a major benefit in having scientists with different but complementary knowledge and technical skills working in close proximity to one another.

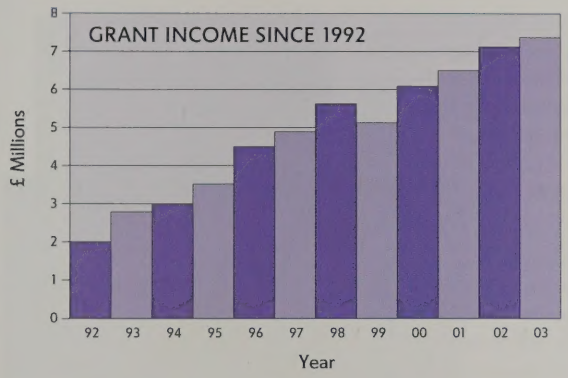
The Institute is an integrated part of Cambridge University, and all Group Leaders are affiliated to a University Department and contribute to teaching and graduate student supervision.

CENTRAL SUPPORT SERVICES

The Institute's 'core staff' provides administrative, technical and computing support to scientists, in order to ensure the smooth running of the Institute. In 2003, as the time for our move to the new building approaches, this has meant supporting the Institute in its present building whilst being involved in detailed planning for the new one to an ever-increasing degree. This juggling act has been performed with typical grace and good humour, and the Institute is grateful to every member of the core team.

In March 2003 Linda Millett, Administrative Assistant and one of the longest-serving members of the core staff, left to join a new Biotech company. We all miss her hard work, enthusiasm, dedication and sense of humour, and wish her well in her new post.





FUNDING

Our two major funding bodies, the Wellcome Trust and Cancer Research UK, continue to offer the Institute vital backing in the form of Fellowships, individual project grants, and programme and equipment grants. In the course of 2004 we will be submitting our applications for renewed funding from 2005 onwards.

Other sources of financial support, both direct and indirect, include the European Community, BBSRC, the MRC, EPSRC, the Royal Society, the Lister Institute, the Elmore Trust, the Isaac Newton Trust, the Leverhulme Trust, Beit Memorial Fellowships, the Association for International Cancer Research, NIH and the European Molecular Biology Organisation. We are extremely grateful to all these organisations for their continuing support.

The University has also been generous in its support of the Institute, particularly in funding equipment for the new building.

RETREAT

Our Annual Retreat was held again at Lady Margaret Hall, Oxford on 25th and 26th September 2003. There was as always a strong attendance and the entire occasion was a success both scientifically and socially. Many thanks to the administrative team and to Magdalena Zernicka-Goetz and Jon Pines for organising it.

Institute Retreat, Lady Margaret Hall, Oxford, September 2003.



JULIE AHRINGER



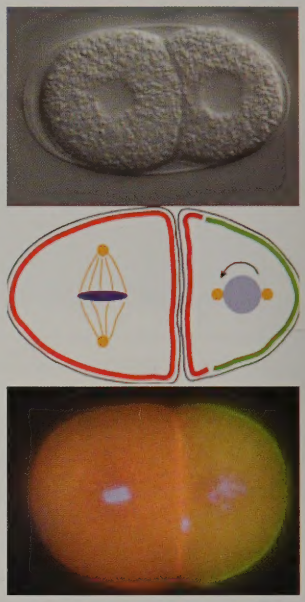
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We study how patterns of cell divisions and cell fates are controlled, using *C. elegans* as a model system. We have focused on two major questions. First, how is cell polarity first established and this information then transduced within the cell for asymmetric cell division? Second, what is the role of chromatin regulation in cell fate decisions? For these studies, we are taking advantage of a genome-wide RNAi library we have constructed.

Cell polarity is an essential feature of most animal cells. The one-celled *C. elegans* embryo is a simple and powerful model system for studying cell polarity and transduction of polarity information for asymmetric cell division. We have shown that heterotrimeric G proteins transmit polarity information to the spindle and have identified many new polarity loci using genome-wide RNAi screening. We study these with a range of techniques, including videomicroscopy of live embryos.

Transcription repression mediated through histone deacetylase (HDAC) complexes is widespread. However, little is known about the developmental roles and regulation of histone deacetylation. One of the major histone deacetylation complexes in animal cells is called NuRD (nucleosomal remodeling and histone deacetylase). In *C. elegans*, the NuRD complex is involved in a range of different processes, including inhibition of Ras signalling. Using genome-wide RNAi screening, we have identified many new chromatin factors that cooperate with NuRD. We are studying the function of these proteins in transcriptional control and their relationships to NuRD and each other using microarrays and other techniques.



C. elegans embryos are highly polarised. The anterior cell is larger than the posterior one (top), and the two cells have different cortical proteins, different spindle orientations, and different cell cycle times (middle and bottom).

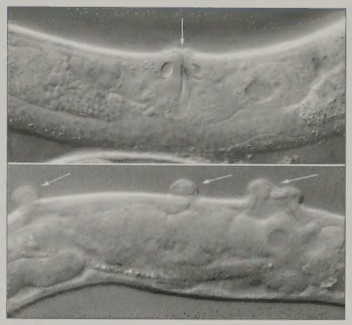
Kamath RS, Fraser AG, Dong Y, Poulin G, Durbin R, Gotta M, Kanapin A, Le Bot N, Moreno S, Sohrmann M, Welchman D, Zipperlen P and Ahringer J (2003) Systematic functional analysis of the *C. elegans* genome using RNAi. **Nature** 421, 231–237

Ahringer J (2003) Control of cell polarity and mitotic spindle positioning in animal cells. **Curr Opin in Cell Biol** 15, 73–81

Gotta M, Dong Y, Peterson YK, Lanier SM, and Ahringer J (2003) Asymmetrically distributed *C. elegans* homologues of AGS3/PINS control spindle position in the early embryo. **Curr Biol** 13, 1029–37

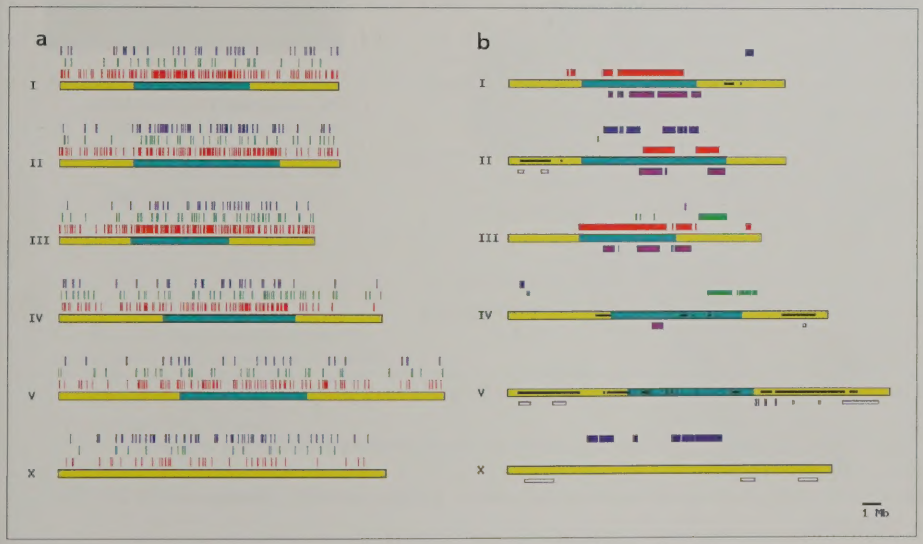
For further publications, see numbers 24, 34, 39, 44, 50, 52, 54, 62 and 75 on pp 49–54.

Ras signalling promotes vulval development and is antagonised by multiple chromatin regulatory complexes including the NuRD histone deacetylase and the TRRAP/TIP60 histone acetyltransferase complexes. Lack of NuRD function results in ectopic vulval tissue in the adult worm (arrows, bottom). Wild type (top).

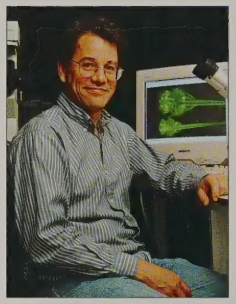




Posterior displacement of the first mitotic spindle (blue-green) is controlled by posterior enrichment of GPR-1/2 proteins (purple), homologs of human AGS3 and *Drosophila* PINS. A complex of GPR-1/2 and Gα subunits control pulling forces acting on the spindle poles.



Genome wide RNAi screening reveals clustering of genes with similar functions
a) Each red, green, and blue tick represents the location of a gene with an RNAi phenotype on one of the six C. elegans chromosomes (yellow), identified in an RNAi screen of 16,757 genes; red (lethal phenotype), green (growth defect), blue (post-embryonic defect).
b) Genes with similar functions are clustered in certain regions of the genome; colours are as for (a). Purple bars show correspondence of clustering of genes with a particular shared transcription profile with that of lethal genes.



Co-Workers:

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Ricardo Costa
Rosalind Friday
Kathy Hartley
Jeffrey Huang
Shoko Ishibashi
Lars Petersen
Jeremy Sivak

One of the main interests of our group is understanding the molecular events responsible for mesoderm formation and patterning. In particular we are investigating the role of fibroblast growth factor (FGF) signalling during mesoderm formation in the frog, *Xenopus laevis*. We have shown that inhibiting FGF signalling during gastrulation disrupts mesoderm formation and morphogenesis. In order to better understand this process, we have begun to isolate downstream targets of FGF signalling. We have identified *Xsprouty2* as one important target gene. This protein and the related proteins, Xsprouty1, Xspred1 and Xspred2 have the interesting property that they are both a target of FGF signalling and modulators of FGF signalling, and they are important in coordinating the movements of gastrulation and mesoderm formation.

In order to identify additional genes involved in mesoderm formation and morphogenesis, we have begun to use bioinformatics approaches in combination with functional screens to identify additional genes involved in these processes. To maximise the efficiency of the functional screen, we have identified over 5000 full-length from *Xenopus tropicalis*. To date we have screened over 2000 of these clones and have identified more than two dozen genes, which alter or inhibit mesoderm formation and/or gastrulation movements.



Tadpole with secondary tail induced by the misexpression of a cytoplasmic tyrosine kinase. This gene was identified in a functional screen for genes involved in mesoderm patterning and morphogenesis.

In addition we are interested in investigating the role of growth factor signalling in patterning of the nervous system. We have begun to study the role for *Xenopus Dachshund* in the patterning of the nervous system as well as neurotrophic factors in the pathfinding of the trigeminal nerve.

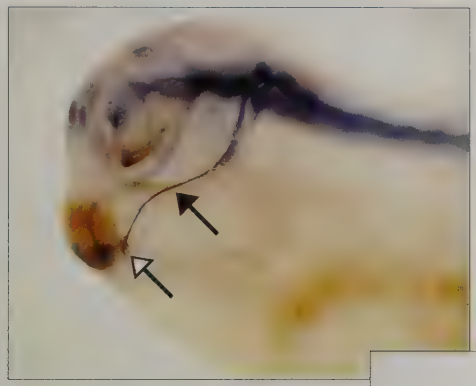
Finally we are performing an insertional mutagenesis screen using a gene trap approach in *Xenopus tropicalis*, a diploid frog related to *Xenopus laevis*, with a view of identifying novel genes involved in development.

Kenwrick S, Amaya E and Papalopulu N (2004) A pilot morpholino screen in *Xenopus tropicalis* identifies a novel gene involved in head development. **Dev Dyn** [in press]

Costa RMB, Mason J, Lee M, Amaya E and Zorn AM (2003) Novel gene expression domains reveal early patterning of the *Xenopus* endoderm. **Gene Expression Patterns** 3, 509–519

Polli MP and Amaya E (2002) A study of mesoderm patterning through the analysis of the regulation of *XMyf-5* expression. **Development** 129, 2917–2927

For further publications, see number 15 on p 50.



Head of transgenic tailbud embryo (stage 28), expressing placental alkaline phosphatase (PLAP) under the control of the neural specific β-tubulin promoter. At this stage the most prominent nerve in the head is the trigeminal nerve (black arrowhead), which innervates the posterior region of the cement gland (white arrowhead).



Head of transgenic tadpole (stage 45), expressing placental alkaline phosphatase (PLAP) under the control of the neural specific β-tubulin promoter. The cranial nerves are easily visualised.

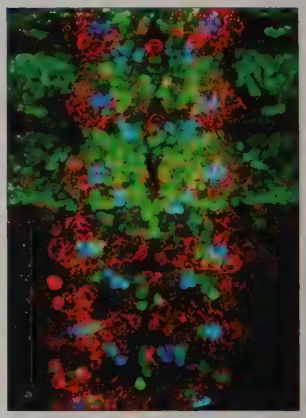
ANDREA BRAND



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Boris Egger
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John Solly
Christine Turner

We are interested in how cellular diversity is generated in the nervous system and in the signalling pathways that direct axon pathfinding and synaptic development. In the *Drosophila* CNS, neurons and glia arise from neural stem cells, or neuroblasts. Neuroblasts renew themselves at each division and give rise to smaller daughter cells called GMCs. Discovering how stem cells are maintained in a multipotent state and how their progeny differentiate into distinct cellular fates is of fundamental importance in understanding development. Our research focuses on how cellular diversity is generated by asymmetric stem cell division. A simple way to generate two different cell types is by the asymmetric partitioning of cell fate determinants. For example, the determinant Prospero is segregated from the neuroblast to its daughter at each division. We have shown that myosins, motor proteins that interact with the actin cytoskeleton, play an integral role in the asymmetric segregation of Prospero. Once in daughter cells, Prospero restricts their mitotic potential. We use time lapse confocal microscopy to follow asymmetric cell division in living embryos, and have fused different spectral variants of GFP to Prospero, Myosin, actin and microtubules for multi-colour labelling *in vivo*. We are also characterising the role in axon pathfinding of the *Drosophila* Ephrin and Fer homologues, using classical and reverse genetic approaches such as ectopic expression and targeted RNAi, to eliminate expression in specific cells. Using similar approaches we have demonstrated a novel function for the anaphase promoting complex in post-mitotic cells: the regulation of synaptic growth and activity.



The embryonic CNS labelled for the homeotic protein Ubx (green), the transmembrane protein sanpodo (red), and the transcription factor even skipped (blue).

For further information please see the Brand lab home page:
http://www.welc.cam.ac.uk/~brandlab

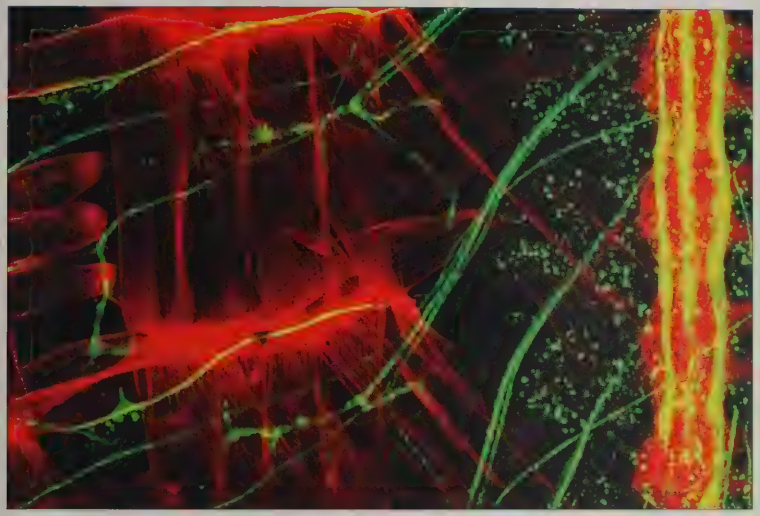
Barros CS, Phelps CB and Brand AH (2004) *Drosophila* nonmuscle myosin II promotes the asymmetric segregation of cell fate determinants by cortical exclusion rather than active transport. **Dev Cell** 5, 829–840

Brand AH and van Roessel PJ (2003) Region-specific apoptosis limits neural stem cell proliferation. **Neuron** 37, 185–187

van Roessel P and Brand AH (2002) Imaging into the future: visualizing gene expression and protein interactions with fluorescent proteins. **Nat Cell Biol** 4, E15–20

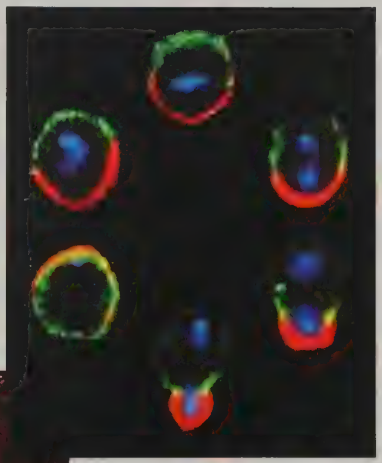
Bossing T and Brand AH (2002) Dephrin, a transmembrane ephrin with a unique structure, prevents interneuronal axons from exiting the *Drosophila* embryonic CNS. **Development** 129, 4205–4218

van Roessel P, Hayward NM, Barros CS and Brand AH (2002) Two-color GFP imaging demonstrates cell-autonomy of GAL4-driven RNA interference in *Drosophila*. **genesis**, 134, 170–173

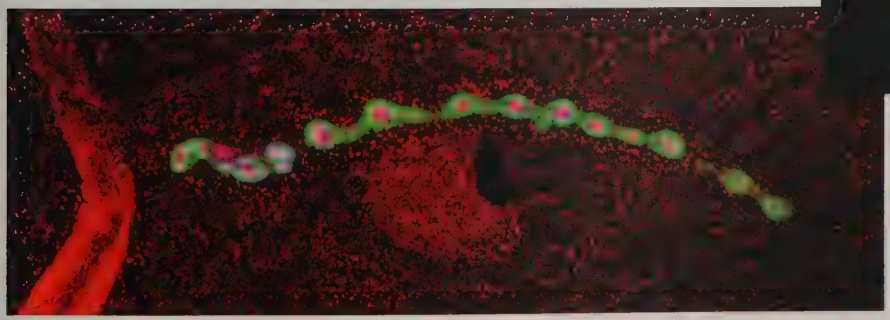


Motor neurons (green, Fasciclin II) exit the CNS and form synapses on specific target muscles (red, phalloidin). Interneurons extend along the longitudinal axon tracts (yellow).

From prophase, myosin II (green) and Miranda (red) localise to opposite sides of mitotic neuroblasts. DNA is in blue.



A ubiquitin ligase concentrates pre-synaptically (purple) at the neuromuscular synapse, where it regulates protein degradation. The post-synaptic membrane is labelled in green and the muscle in red.



NICK BROWN

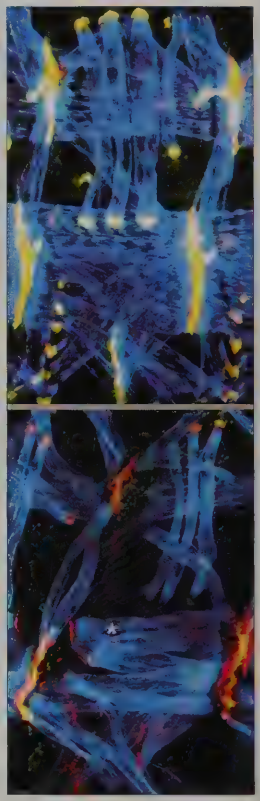


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Guy Tanentzapf
Cathy Torgler
Vikki Williams
Christos Zervas

Cellular adhesion and communication are vital during the development of multicellular organisms. These processes use proteins on the surface of cells, which stick cells together or transmit signals from outside the cell to the interior, so that the cell can respond to its environment. Members of one family of cell surface receptors, called integrins, can perform both of these activities, and therefore provide a molecular link between cell adhesion and signalling. Our research is focused on determining how proteins inside and outside the cell assist the integrins in their developmental roles: mediating cell migration, adhesion between cell layers and cell differentiation.

We have used the genetics of the fruit fly *Drosophila* to identify proteins that work with integrins in the developing animal. The molecular characterisation of these proteins is revealing how integrins provide a stable link between the extracellular matrix and the cytoskeleton. Among the approximately 30 genes identified are those encoding two cytoskeletal linker proteins, talin and a spectraplakin called short stop, and two signalling adaptor proteins, integrin linked kinase and tensin. By manipulating the structure of these proteins and assaying their function in the living animal we are elucidating how they contribute to integrin-mediated adhesion during development. Highlights of this past year include the characterisation of a new stabilising function for tensin on integrin adhesive complexes, and the discovery of novel functions for short stop in cell-cell adhesion and microtubule organisation.



Bökel C and Brown NH (2002) Integrins in development: moving on, responding to, and sticking to the extracellular matrix. **Dev Cell** 3, 311–321

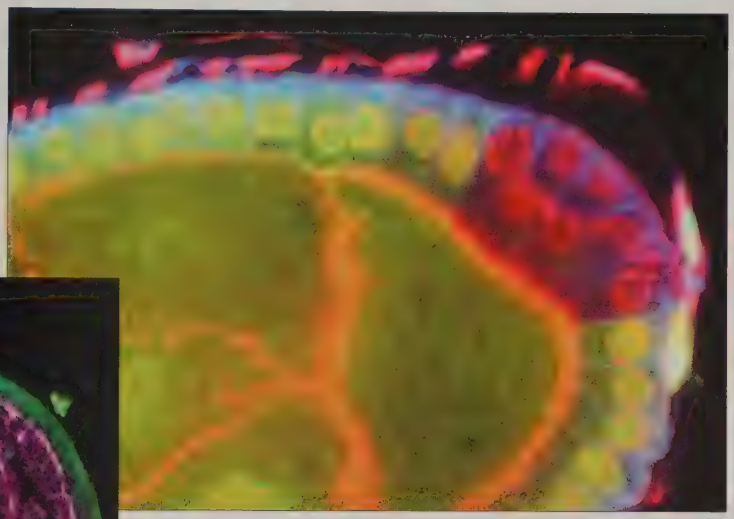
Brown NH, Gregory SL, Rickoll WL, Fessler LI, Prout M, White RAH and Fristrom JW (2002) Talin is essential for integrin function in *Drosophila*. **Dev Cell** 3, 569–579

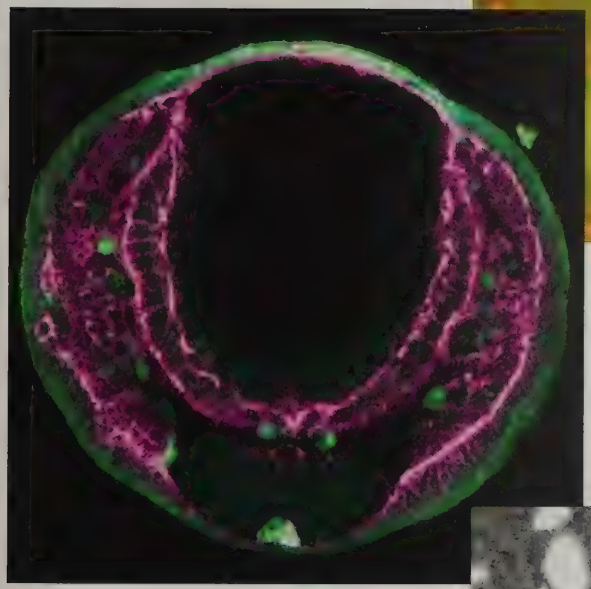
Röper K and Brown NH (2003) Maintaining epithelial integrity: a function for gigantic spectraplakin isoforms in adherens junctions. **J Cell Biol** 162, 1305–1315

Torgler CN, Narasimha M, Knox AL, Zervas CG, Vernon MCH and Brown NH (2004) Tensin stabilises integrin adhesive contacts in *Drosophila*. **Dev Cell** [in press]

Röper K and Brown NH (2004) A spectraplakin is the fusome component that organises microtubules during oocyte specification in *Drosophila*. **Curr Biol** [in press]

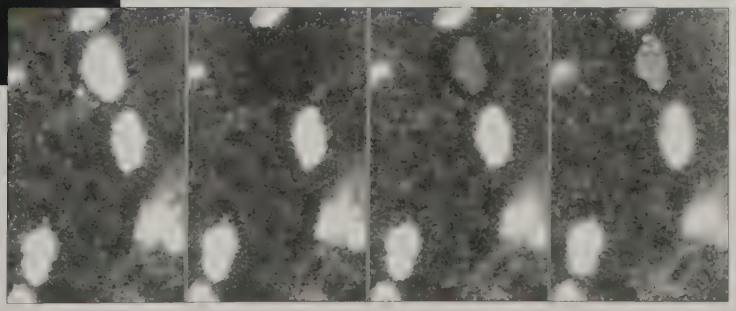
Facing page: Integrins mediating the attachment of the muscles to the body wall of the Drosophila embryo (top). When integrins (green) are reduced in the muscles (bottom), the cytoskeletal linker protein talin (red; overlap with integrins appears yellow) and the muscle cytoskeleton (blue) detach from the integrins (especially visible in the muscles marked with an asterisk)





Integrin distribution (purple) viewed during the morphogenetic process of dorsal closure.

The cells within the follicular epithelium, which surround the central group of large nurse cells and the oocyte, require spectraplakin function to maintain a monolayer. A group of cells lacking the spectraplakin (absence of green) have formed two layers



Dynamics of the association of fluorescently labelled tensin with integrin adhesive complexes, as monitored by fluorescence recovery after photobleaching.

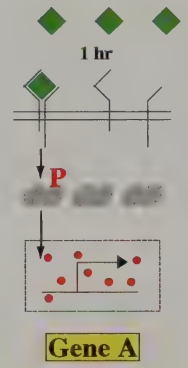


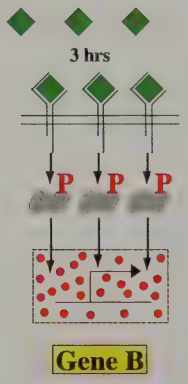
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Ray Kit Ng
Ilenia Simeoni
Stina Simonsson
Caroline Webb

Our group is interested in nuclear reprogramming and cell fate determination by signal factors in amphibian development. We have the long-term aim of establishing a route for the production of replacement cells of the same genetic composition as the donor cells used. Many different cell-types can be generated by transplanting the nucleus of a specialised cell to an enucleated egg by which it is reprogrammed. We have recently found that mouse and human blood cell nuclei are induced to express the stem cell marker gene oct4 when they are injected into growing amphibian oocytes. Unlike eggs, oocytes do not induce DNA replication and can therefore reprogram adult cell nuclei directly. Amphibian oocytes are therefore particularly well suited to our current attempts to understand mechanisms of nuclear reprogramming and to identify the molecules responsible.

Early embryonic cells, whether obtained by fertilisation or by nuclear transfer, can be made to embark on diverse cell differentiation pathways by exposure to an appropriate concentration of signal factors such as activin or BMP4. We are analysing the mechanisms by which cells can recognise and respond to small changes in the extracellular concentration of these signal factors. We find that critical aspects of recognition of extracellular signal factor concentration include the steady state concentration of Smad2 in the nucleus, and the ability of cells to memorise a particular level of receptor occupancy after the removal of extracellular signal factor. We follow the real-time movement of GFP-Smad2 to understand how receptor occupancy leads to a particular rate of flow of activated smad2 to the nucleus, and hence to an appropriate direction of embryo cell fate.





Freeman M and Gurdon JB (2002) Regulatory principles of developmental signalling. **Annu Rev Dev Biol** 18, 515–539

Gurdon JB and Byrne JA (2003) The first half-century of nuclear transplantation. **Proc Natl Acad Sci USA** 100, 8048–8052

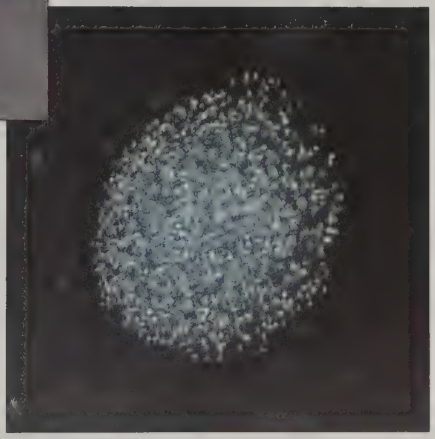
Byrne JA, Simonsson S, Western PS and Gurdon JB (2003) Nuclei of adult mammalian somatic cells are directly reprogrammed to oct-4 stem cell gene expression by amphibian oocytes. **Curr Biol** 13, 1206–1213

Gurdon JB, Bryne JA and Simonsson S (2003) Nuclear reprogramming and stem cell creation. **Proc Natl Acad Sci USA** 100, 8048–8052

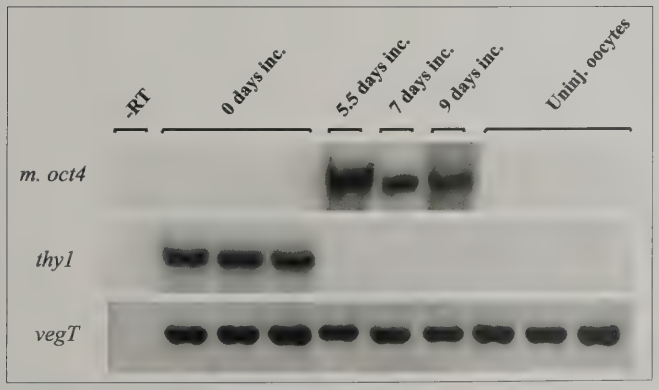
Facing page: Morphogen gradient interpretation depends on the steady-state concentration of activated Smad2 (red spots) in the nucleus. A low concentration induces gene A, and a higher concentration induces gene B. Extracellular ligand binds to receptors which phosphorylate cytoplasmic Smad2 (grey ovals with red P).



Growing oocytes of *Xenopus laevis*. Each oocyte contains a very large nucleus (the 'germinal vesicle').



An isolated germinal vesicle of a *Xenopus* growing oocyte. The bright spots are oocyte nucleoli containing transcriptionally active ribosomal RNA genes.



Xenopus oocytes injected with mouse thymocyte nuclei induce expression of the stem cell marker m.oct4, and extinguish expression of the thymocyte-specific gene thy-1.



Co-workers:

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Michal Goldberg
Serge Gravel
Muriel Grenon
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Alicia Lee
Christine Magill
Abdel Moumen
Venkat Pisupati
Philip Reaper
Helen Reed
Alex Sartori
Philippa Smith
Veronique Smits
Manuel Stucki

It is crucial for cells to maintain genome stability despite unrelenting attack by both environmentally-derived and endogenously-generated DNA damaging agents. We are trying to understand how mammalian and yeast cells achieve this by sensing DNA damage and transducing this information to the DNA repair and cell cycle machineries (Figure 1). We are also investigating how these events are elicited under other biological circumstances, and how defects in these pathways can trigger human pathology.

Over the past year, we have discovered that the novel human protein, MDC1, functions in the intra-S phase DNA-damage checkpoint and plays a key role in orchestrating the accumulation of DNA repair and checkpoint proteins at sites of DNA-damage (Figure 2). Furthermore, we have established that DNA-damage responses are triggered by short telomeres in human cells undergoing replicative senescence (Figures 3 and 4), and that the senescent state requires the continued actions of DNA-damage checkpoint kinases. These latter findings establish the molecular basis for replicative senescence and have implications for cancer – where cells generally escape senescence – and other age-related diseases.

We are also continuing to investigate how DNA-damage responses are influenced by chromatin structure. For example, we have found that the yeast histone deacetylase component, Sin3p, is required for effective DNA repair by non-homologous end-joining. Furthermore, with our collaborator, Jessica Downs (Department of Biochemistry, Cambridge University), we have discovered that the yeast linker histone, Hho1p, suppresses DNA repair by homologous recombination. One of our aims over the coming year will be to extend these yeast findings to human cells.

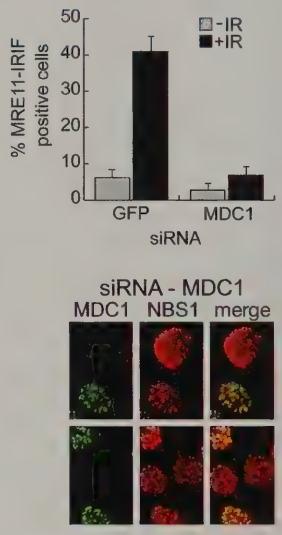


Fig 2: MDC1 is required to recruit the MRN complex to foci at sites of DNA damage. Cells where MDC1 expression was knocked down using siRNA are unable to form MRN foci following treatment with radiation.

Goldberg M, Stucki M, Falck J, D'Amours D, Rahman D, Pappin D, Bartek J and Jackson SP (2003) MDC1 is required for the intra-S-phase DNA damage checkpoint. **Nature** 421(6926), 952–956

d'Adda di Fagagna, F, Reaper PM, Clay-Farrace L, Fiegler H, Carr P, von Zglinicki T, Saretzki G, Carter NP and Jackson SP (2003) A DNA damage checkpoint-mediated response in telomere-initiated cellular senescence. **Nature** 426 (6963), 194–198

Downs JA, Kosmidou E, Morgan A and Jackson SP (2003) Suppression of homologous recombination by the Saccharomyces cerevisiae linker histone. **Mol Cell** 11(6), 1685–1692

For further publications, see numbers 4, 5, 6, 13, 16, 18, 28, 33, 57 and 63 on pp 49–54.

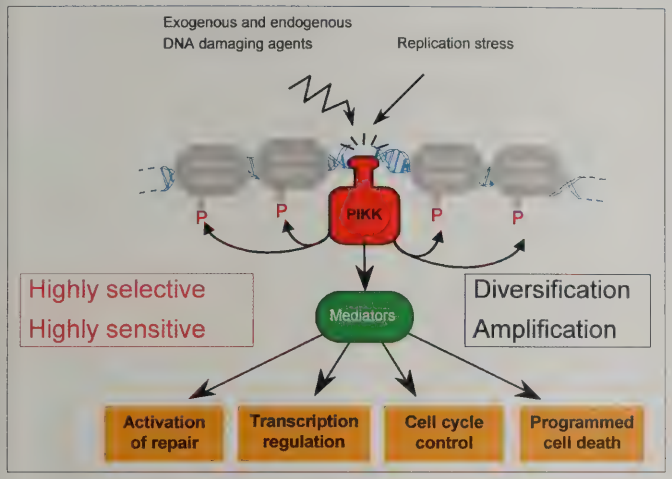
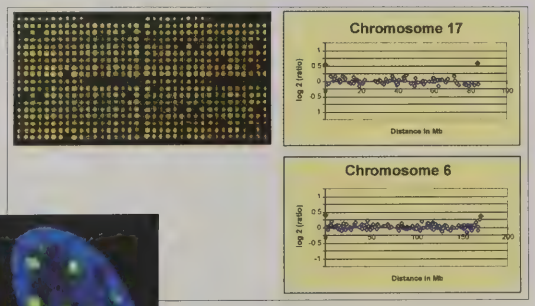


Fig 1: Cellular responses to DNA damage. DNA damage is detected by a sensor or sensors that then triggers the activation of a kinase cascade via PIKKs (PI3-kinase like kinases) such as DNA-PKcs, ATM and ATR. These are recruited to sites of DNA damage and phosphorylate downstream targets such as Chk1, Chk2 and the MRN complex leading to a range of cellular responses.

Fig 4: γ-H2AX was shown to be specifically associated with the telomeres of chromsomes in senescent cells as determined by probing whole-genome DNA microarrays with immune precipitated material. Clones showing significantly enhanced signals in senescent cells are coloured red. This work was done in collaboration with Nigel Carter and Heinke Fiegler (Wellcome Trust Sanger Institute).



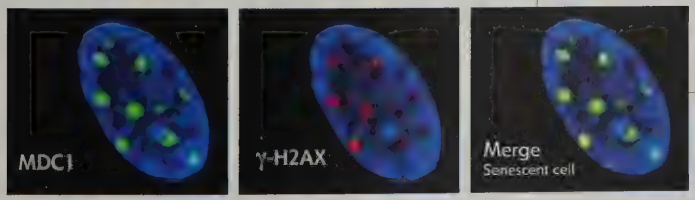


Fig 3: DNA double-strand break response factors such as MDC1 co-localize with γ-H2AX (a marker of DNA damage) in senescent cells to form a novel subnuclear structure termed SDF (senescence-associated DNA damage focus).

TONY KOUZARIDES



Co-workers:

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Luke Hughes-Davies
Paul Hurd
David Lando
Susana Lopes
Steven Sanders
Helena Santos Rosa
Robert Schneider

Many transcriptional regulators are de-regulated in cancer. Our group is interested in defining the mechanisms by which such transcription factors function during normal cell proliferation and in cancer.

Our attention is focused on a set of enzymes (acetylases, deacetylases, methylases and kinases) which regulate transcription by covalently modifying histones. We would like to understand what biological processes these enzymes control and the precise mechanism by which histone modification affects chromatin function. In addition, a number of chromatin modifying enzymes have been implicated in the genesis of cancer so we are interested in the pathways misregulated in cancer cells.

Our work on lysine methylation has shown that methylation of lysine 4 of histone H3 functions by recruiting the chromatin remodelling ATPase Isw1p. Investigation of arginine methylation has revealed that this modification is "communicating" with acetylation: methylation of arginine by CARM1 is dependent on prior acetylation of adjacent residues by CBP.

We have identified a novel factor, EMSY, which binds to the product of BRCA2, a gene found deleted in familial breast and ovarian cancer. EMSY associates with the chromatin regulator HP1 and has a role to play in transcription and DNA repair, just like BRCA2. Remarkably we find that the EMSY gene is amplified specifically in sporadic cases of breast and ovarian cancer. The physical, functional and clinical relationships between EMSY and BRCA2 strongly suggest that the pathways they regulate are linked.



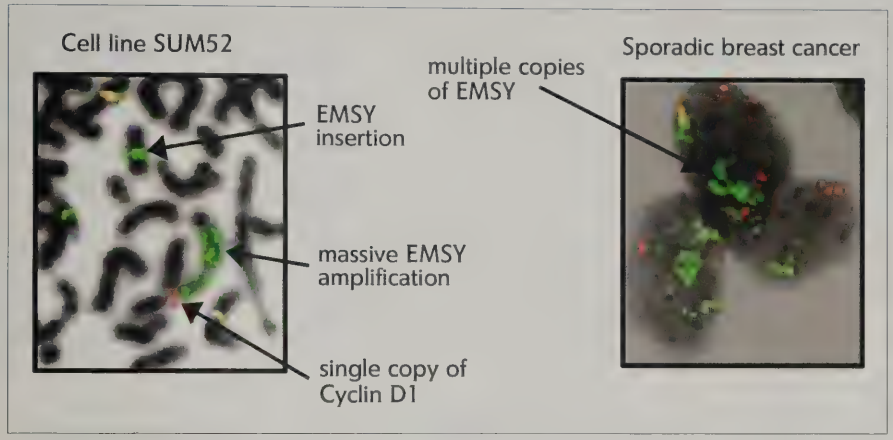
EMSY co-localises with g-H2AX a marker for sites of DNA repair.

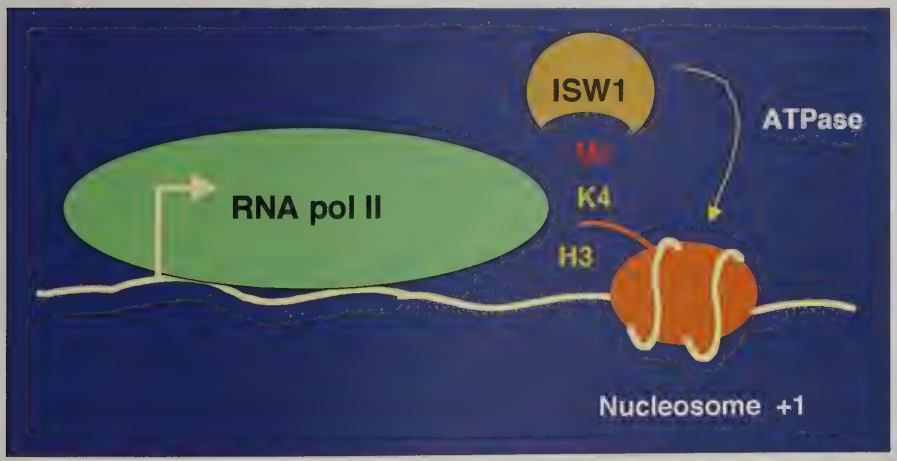
Hughes-Davies L, Huntsman D, Ruas M, Fuks F, Bye J, Chin SF, Milner J, Brown LA, Hsu F, Gilks B, Nielsen T, Schulzer M, Chia S, Ragaz J, Cahn A, Linger L, Ozdag H, Cattaneo E, Jordanova ES, Schurring E, Yu DS, Venkitaraman A, Ponder B, Doherty A, Aparicio S, Bentley D, Theillet C, Ponting CP, Caldas C and Kouzarides T (2003) EMSY Links the BRCA2 Pathway to Sporadic Breast and Ovarian Cancer. **Cell** 115, 523–535

Santos-Rosa H, Schneider R, Bernstein B, Karabetson N, Morillon A, Weise C, Schreiber SL, Mellor J and Kouzarides T (2003) Methylation of histone H3 K4 mediates association of ISW1p ATPase with chromatin. **Mol Cell** 12 (5), 1325–1332

For further publications, see numbers 22, 41and 61 on pp 49–54.

The EMSY gene is found amplified in breast cancer cell lines and in primary sporadic breast cancers.
(Collaboration with Carlos Caldas)





Model of how methylation of K4 on Histone H3 regulates transcription. Methylation recruits the ISW1 ATPase
This in turn remodels chromatin around nucleosome plus 1 and allows correct positioning of RNA polymerase II



Co-workers:

Juliet Barrows
Sabhi Rahman
Stephen Sansom
James Smith
Uruporn Thammongkol

The neocortex is the part of the brain that is responsible for cognition, perception and the control of movement. It is also a region of the nervous system unique to mammals. The neocortex is a sheet-like structure composed of six layers of neurons that are generated in order over a six day interval during development of the mouse brain. However, the neocortex is a modular structure, composed of anatomically distinct areas. These areas have different incoming and outgoing connections to other parts of the brain, and are primarily dedicated to different functions, including motor control and the somatic senses. We are applying genomics and systems biology approaches to answering two questions: how is the temporal order of neurogenesis controlled in the developing neocortex, and how is the adult pattern of neocortical areas generated during development. The two most significant evolutionary changes in the neocortex are an increase in the size of the neocortex relative to other brain structures, and an increase in the number of functional areas. Our aim is to use our understanding of cortical development in one organism as the basis for comparative evolutionary studies of cortical area formation in other mammals.

Examples of our current research include:

1) Studying the genetic basis for the formation of functional areas of the neocortex;

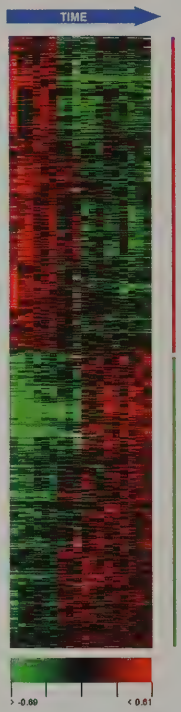
2) Characterising the transcriptional responses of neocortical progenitor cells to extracellular factors implicated in patterning the neocortex;

3) Identifying the *in vivo* targets of transcription factors required for cortical development;

4) Defining the genetic networks involved in laminar (cell layer) cell fate determination in the neocortex;

5) Classifying cortical neurons by single cell expression profiling;

6) Gain and loss of function studies of genes identified by these approaches *in vivo* and using *in vitro* model systems of cortical development.



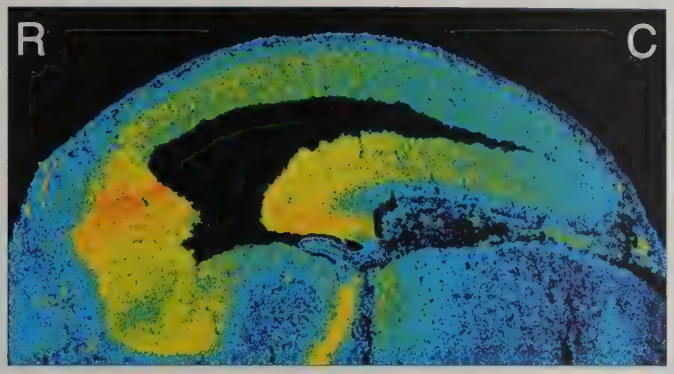
Temporal gene expression in the neocortex. Cluster shows genes that increase (transition from green to red) and decrease (transition from red to green) in expression over the six days of neurogenesis.

Livesey R (2002) Have microarrays failed to deliver for developmental biology? **Genome Biol** *3*, 2009.1–2009.5.

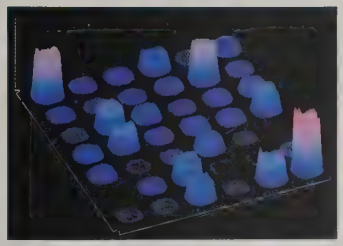
Livesey FJ (2003) Strategies for microarray analysis of limiting amounts of RNA. **Briefings in Functional Genomics & Proteomics** (2) 1, 31-36.

Livesey FJ, Young TL and Cepko CL (2004). An analysis of the gene expression program of mammalian neural progenitor cells. **PNAS** 101, 1374–1379

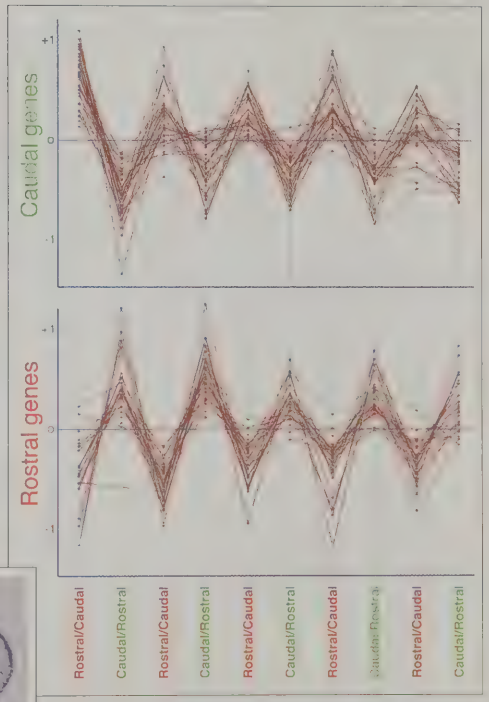
For further publications, see numbers 21 and 59 on pp 49–54.



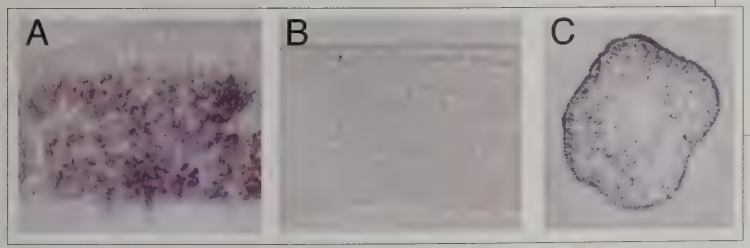
A rostrocaudal gradient of gene expression in the developing neocortex. Fluorescent *in situ* hybridisation on a parasagittal section of the developing neocortex shows strong rostral (R) expression that is absent caudally (C).



Surface plot of a small region of a mouse microarray. Spot height is proportional to the hybridisation intensity.

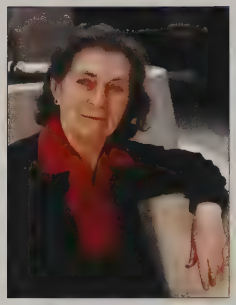


Spatial differences in gene expression in the developing neocortex. Plots of gene expression clusters showing genes enriched in expression at the front (rostral) and back (caudal) of the developing neocortex.



Temporally regulated expression of a transcription factor in the developing neocortex. This gene is expressed in neocortical progenitor cells early in development (A) and is downregulated in progenitor cells two days later (B), a time at which it is highly expressed in other neural structures, such as the retina (C).

ANNE McLAREN



Co-Workers:

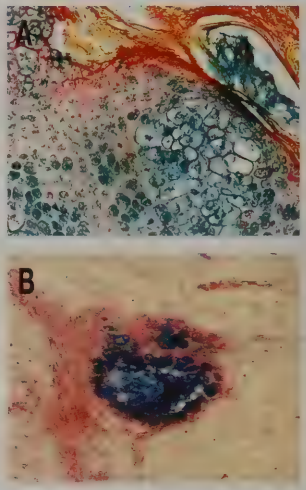
Ian Adams
Dilly Bradford
Gabriela Durcova-Hills

Our research focuses on mouse primordial germ cells (PGCs), the epigenetic changes that they undergo, and the pluripotent stem cells derived from them.

A genetic screen of PGCs has uncovered a novel gene, *mRif1*, orthologous to a yeast family of telomere-associated proteins. Highly expressed in early mouse embryos and pluripotent stem cell lines as well as in germ cells, *mRif1* may be involved in the maintenance of telomere length and perhaps also in pluripotency. Our screen has also identified a gene expressed in the male genital ridge that may play a role in the block to meiosis that germ cells in the male genital ridge undergo.

Our embryonic germ cell (EGC) lines derived from germ cells both before and after entry into the genital ridges show almost complete erasure of site-specific methylation in imprinted genes. This suggests that the methylation status of EGCs does not necessarily reflect that of the PGCs from which they were derived. Since chimeras made with these demethylated EGCs show some skeletal abnormalities, we are carrying out molecular studies on cartilage and bone differentiated from the EGCs *in vitro*.

The only site-specific methylation detected in imprinted genes in these largely demethylated EGCs is in *H19* and *Igf2*, and only in EGCs derived from male embryos. To determine the relative role of chromosomal and gonadal sex, we have made EGC lines from sex-reversed (XY female and XX male) as well as from control embryos. We see the anomalous methylation only in the XY EGC lines, whether they are derived from male or female genital ridges. We are now looking at PGC imprinting in XY female mice.



Differentiation of EGCs in vivo. Histological analysis of tumors formed by EGCs. A, Cartilage (blue staining) B, Secretory epithelia (blue staining)

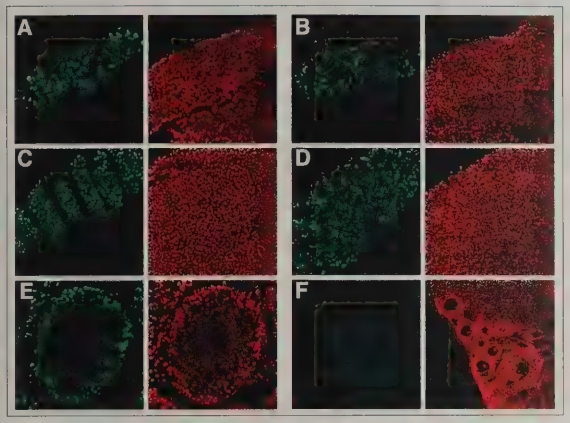
Durcova-Hills G, Wianny F, Merriman J, Zernicka-Goetz M and McLaren A (2003) Developmental fate of embryonic germ cells (EGCs), *in vivo* and *in vitro*. **Differentiation** 71, 135–141

McLaren A (2002) Human embryonic stem cell lines: socio-legal concerns and therapeutic promise. **C R Biologies** 325, 1009–1012

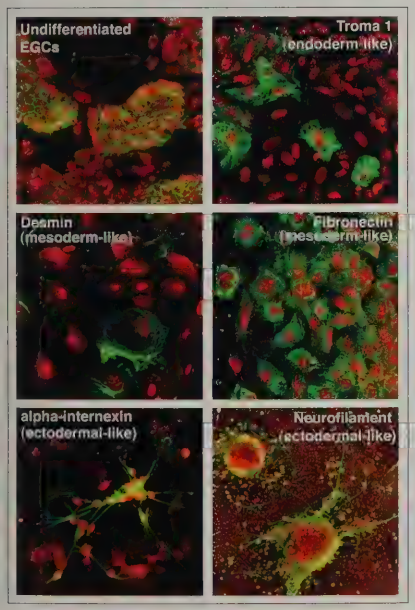
McLaren A (2003) Primordial germ cells in the mouse. **Dev Biol** 262, 1–15

Adams IR and McLaren A (2003) Identification and characterisation of *mRif1*: a mouse telomere-associated protein highly expressed in germ cells and embryo-derived pluripotent stem cells. **Dev Dyn** [in press]

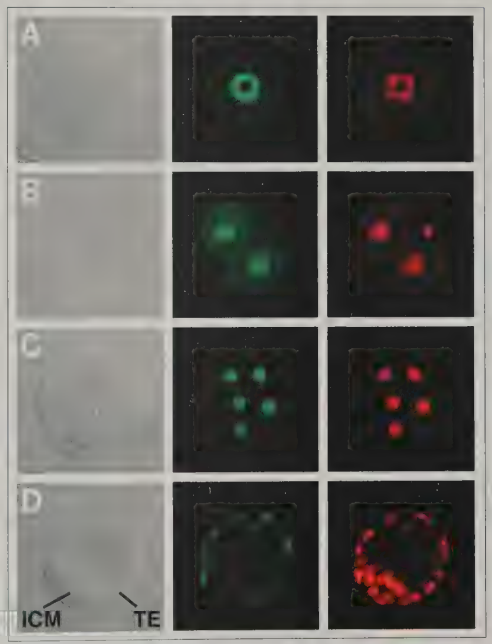
For further publications, see number 19 on p 50.



Staining of mRif1 (green) and DNA (red) showing that mRif1 protein is present in the nuclei of male (A,C,E) and female (B,D,F) germ cells in embryonic gonads before (A,B) and after (C,D) sexual differentiation. mRif1 is also present in the nuclei of germ cells in adult gonads (E,F)



EGCs derived with different FGFs differentiate in vitro into endo-, ecto-, and mesodermal cell lineages.



Staining of mRif1 (green) and DNA (red) showing that mRif1 protein is present in the nuclei of oocytes (A), cleavage stage embryos (B,C), and the trophectoderm (TE) of blastocysts (D).

NANCY PAPALOPULU



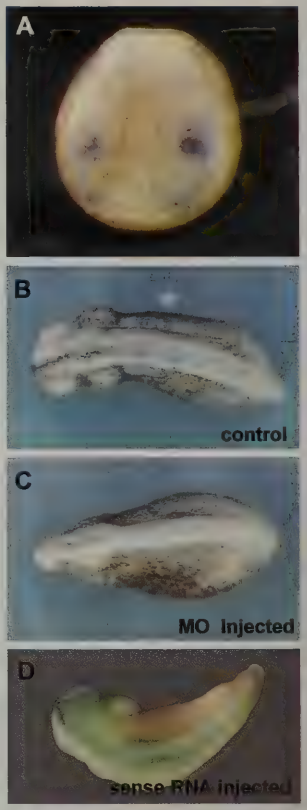
Co-Workers:

Eva Asscher
Juliet Barrows
Andrew Chalmers
Kim Goldstone
Julia Mason
Tarik Regad
Bernhard Strauss
Jana Voigt

During embryonic development, neuroectodermal cells exit the cell cycle and differentiate in a stereotypical spatial and temporal pattern. The spatial and temporal control of neurogenesis is important for regulating cell type specification and the final number of differentiated cells. To understand how this control is achieved, we use the frogs *Xenopus laevis* and *Xenopus tropicalis* as model systems and a combination of molecular and classical embryology.

We are interested in the mechanisms that exert positive and negative control on neuronal differentiation. We are studying the regulation exerted by cell cycle inhibitors such as $p27^{Xic1}$ and regional transcription factors, such as *XBF-1*. We have found that neuronal differentiation is additionally controlled by the intrinsically different capacities of progenitor cells to differentiate. Recently, we have discovered that this intrinsic difference is the result of asymmetric cell divisions that take place at the blastula stage. These divisions generate inner and outer cells and segregate membrane-localised aPKC to the apical membrane of the outer cells. Outer and inner cells become late and early differentiating progenitors respectively; the role of aPKC in this decision is currently being investigated. The long term fate of the late-differentiating progenitors is investigated by single cell labelling. A microarray screening project is also under way to identify novel determinants involved in making outer cells different from inner ones; so far, several inner and outer cell specific genes have been identified.

In parallel, gain and loss of function screens, based on a *X. tropicalis* EST project, have begun to uncover novel genes that affect neural development.



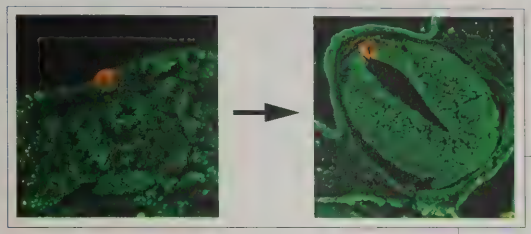
Kenwrick S, Amaya E and Papalopulu N (2004) A pilot morpholino screen in *Xenopus tropicalis* identifies a novel gene involved in head development. **Dev Dyn** [in press]

Chalmers AD, Strauss B and Papalopulu N (2003) Oriented cell divisions asymmetrically segregate aPKC and generate cell fate diversity in the early *Xenopus* embryo. **Development** 130, 2657–68

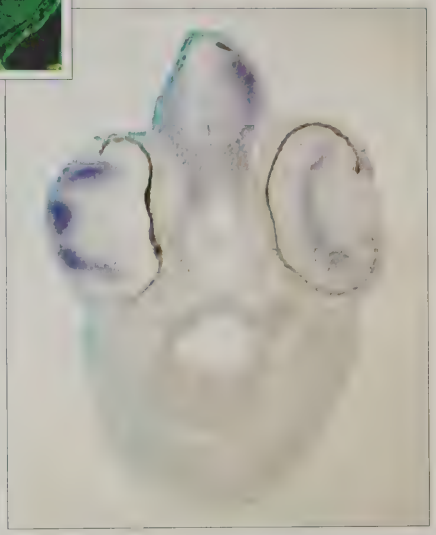
Carruthers S, Mason J and Papalopulu N (2003) Depletion of the cell cycle inhibitor $p27^{Xic1}$ prevents neuronal differentiation and increases the number of neural progenitor cells in *Xenopus tropicalis*, **Mech Dev** 120, 607–16

For further publications, see number 15 on p 50.

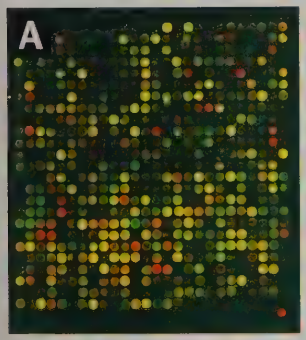
Facing page: A novel gene, expressed in the anterior neural plate (A) as identified in a loss-of-function screen as a gene necessary for forebrain development. Morpholino (MO) mediated knockdown causes a dramatic narrowing of the head (C) compared to the control (B). mRNA injection has the opposite effect (D)



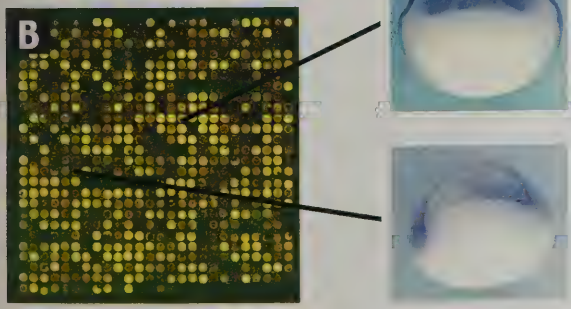
A single outer layer cell injected at the neura plate stage (left panel) with fluorescent dextran and its descendants in the neural tube (right panel)



Overexpression of Cullin, a gene identified in a gain of function screen, increases the number of retinal ganglion cells in the eye (purple). Overexpressing side: light blue



Microarray analysis of early versus late embryo (A) and inner versus outer ectodermal cells of a gastrula embryo (B). Note than relatively fewer differences are detected in B versus A, nevertheless several genes with specific expression in the inner or outer ectodermal layer have been identified with this analysis (right)





A blastomere from a 64 cell stage embryo showing the polarisation. aPKC is localised to the apical side of the cell's membrane (red) while integrin is found basolaterally (green)

JONATHON PINES



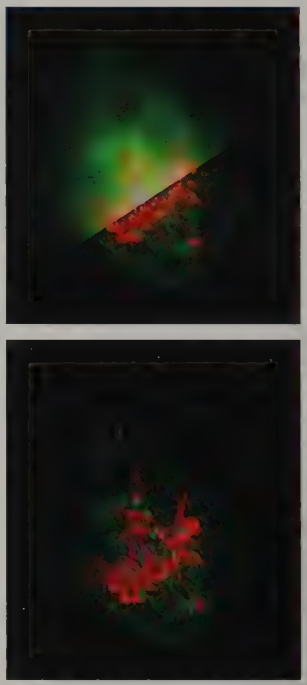
Co-workers:

Claire Acquaviva
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Fay Cooke
Barbara Di Fiore
Alex Domin
Anja Hagting
Mark Jackman
Lars Koop
Catherine Lindon
Takahiro Matsusaka
Jo Richardson
Adam Walker

We are studying how cells divide and focusing on two main aspects of cell division: how the cell first initiates mitosis, and how the cell co-ordinates mitosis by ubiquitin-mediated proteolysis via the APC/C ubiquitin ligase. Because mitosis is a highly dynamic process we are studying these processes in real time by time-lapse fluorescence microscopy. We use FRAP and photo-activation to gain a better understanding of the kinetics of protein behaviour, deconvolution to improve the spatial resolution and FRET to assay protein-protein interaction and kinase activity.

To understand how cells first initiate mitosis we are analysing the behaviour of the mitotic cyclin-CDKs, cyclins A and B1, and their regulation by phosphorylation and subcellular localisation. We use GFP-fusion proteins to determine how localisation is altered depending on the stage of the cell cycle, and to define the domains of the proteins that target them to specific subcellular structures. To identify the proteins responsible for targeting we are analysing protein complexes by mass spectrometry.

To understand how proteolysis is used to regulate progress through mitosis we assay the degradation of the GFP-fusion proteins in living cells. We are studying the behaviour of key APC/C substrates at each stage of mitosis to define the events and the mechanisms that trigger the destruction of specific proteins at specific times, and how this coordinates chromosome segregation and cytokinesis. We are also investigating whether the ubiquitination machinery is spatially regulated in mitosis; in particular whether this is responsible for the exquisite control of protein degradation by the spindle assembly checkpoint.



Top: HeLa cells stained for the APC/C (green), centromeres (blue) and DNA (red). The image on the bottom half is derived by deconvolution from the one on the top half.
Bottom: fully deconvolved image.

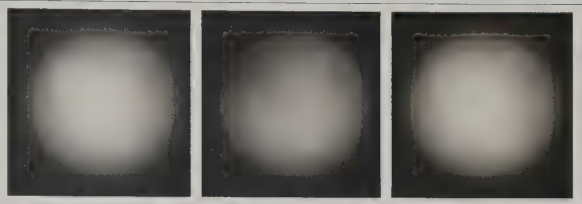
Jackman M, Lindon C, Nigg EA and Pines J (2003) Active cyclin B1-Cdk1 first appears on centrosomes in prophase. **Nature Cell Biol.** 5, 143–148

Hagting A, den Elzen N, Vodermaier HC, Waizenegger IC, Peters J-M and Pines J (2002) Human securin proteolysis is controlled by the spindle checkpoint and reveals when the APC/C switches from activation by Cdc20 to Cdh1. **J Cell Biol** 157, 1125–1137

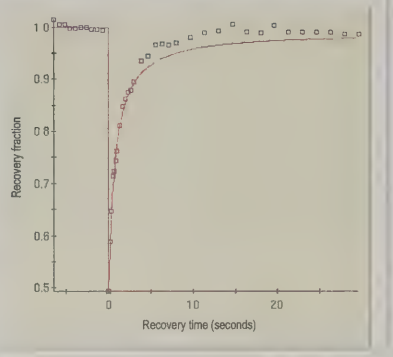
Jackman M, Kubota Y, den Elzen N, Hagting A and Pines J (2002) Cyclin A- and cyclin E-CDK complexes shuttle between the nucleus and the cytoplasm. **Mol Biol Cell** 13, 1030–1045

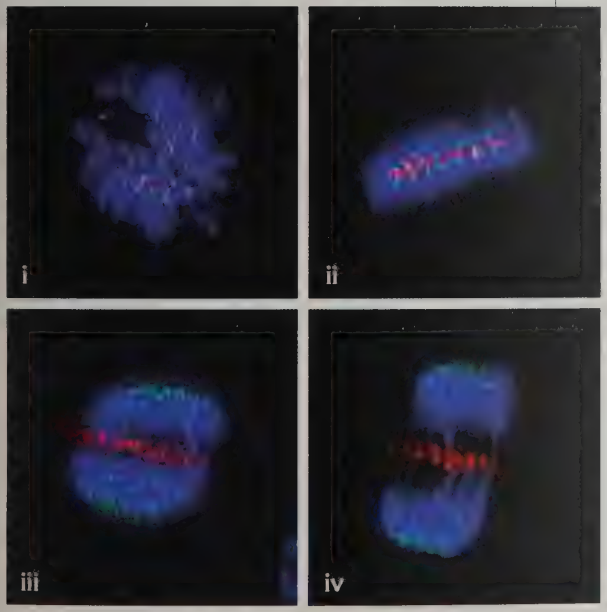
For further publications, see number 40 on p 52.

FRAP (fluorescence recovery after photobleaching): HeLa cells expressing cyclin B1 linked to GFP. One spindle pole was irradiated with 488 nm laser light (middle panel) and the cell imaged using a GFP filter set. Cyclin B1 fluorescence recovers at the spindle pole within 6 secs (right panel).



Recovery of Cyclin B1-GFP on Spindle Poles





Linking Mitosis with Cytokinesis: HeLa cells stained for centromeres (green), DNA (blue) and Aurora B (red) in i) prometaphasephase ii) metaphase iii) anaphase A and iv) anaphase B. Aurora B appears to be important in both the spindle checkpoint and in setting up cytokinesis.

JORDAN RAFF



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The centrosome is the main microtubule organising centre in animal cells. Using *Drosophila* as a model system, we have isolated proteins that bind to microtubules *in vitro* and associate with centrosomes *in vivo*. We hope that by studying these centrosomal microtubule-associated proteins (MAPs) we will better understand how centrosomes interact with microtubules. One such protein, D-TACC, interacts with microtubules via its association with Minispindles (Msps), the *Drosophila* homologue of XMAP215. This interaction is highly conserved, and TACC proteins appear to stabilise centrosomal microtubules by recruiting Msps/XMAP215 to centrosomes in flies, frogs, worms, and humans. Another centrsomal MAP, CP190, binds directly to microtubules, but is not involved in regulating centrosomal microtubules. Instead, it is involved in regulating myosin function in the early Drosophila embryo.

How are centrosomal proteins like D-TACC and CP190 recruited to centrosomes? We find that the *Drosophila* Pericentrin-like protein (D-PLP) is most strongly concentrated in the centrioles, the complex microtubule structures that lie at the heart of the centrosome. In *D-plp* mutant cells, the recruitment of many centrosomal markers, such as D-TACC, CP190, and γ-tubulin, is disrupted, suggesting that D-PLP is essential for the recruitment of many, if not all, components of the PCM. Surprisingly, however, mitosis occurs relatively normally in *D-plp* mutant cells, and *D-plp* mutants are viable, but uncoordinated. We have found that D-PLP is essential for proper cilia formation, and *D-plp* mutants are uncoordinated because the cilia of the mechanosensory neurons are non-functional.



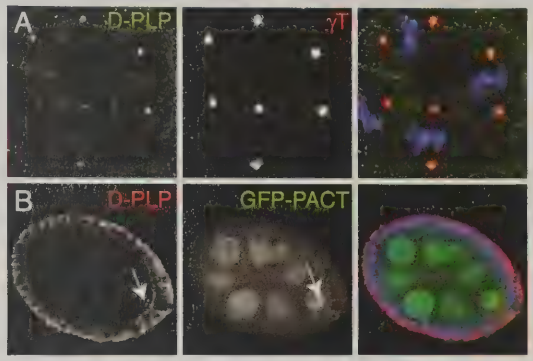
The D-TACC/Msps complex is concentrated at centrosomes, and also in punctate dots that decorate the spindle microtubules. The distribution of Msps (red), microtubules (green) and chromosomes (blue) is shown in embryos where the nuclei have entered anaphase.

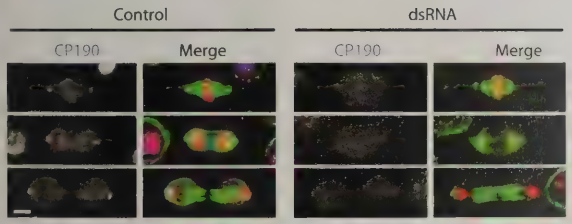
Butcher RDJ, Chodagam S, Basto R, Wakefield JD, Henderson DS, Raff JW, and Whitfield WGF (2003) The *Drosophila* centrosome-associated protein CP190 is essential for viability, but not for cell division. **J Cell Sci** [in press]

Raff JW (2003) Genome maintenance. **Nature** 423, 493–495

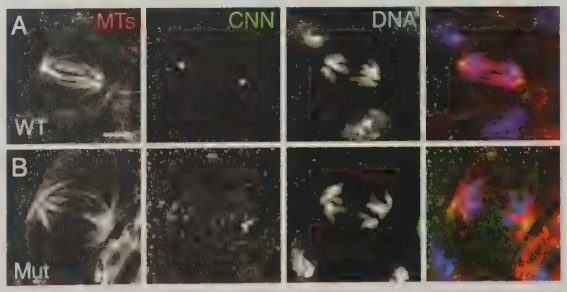
Gergely F, Mythily V, Lee M and Raff JW (2003) The ch-Tog/XMAP215 protein is essential for spindle pole organisation in human somatic cells. **Genes and Dev** 17, 336–341







The centrosomal MAP CP190 does not appear to regulate the behaviour of centrosomal microtubules during mitosis. Drosophila tissue culture cells were either treated with mock dsRNA (left hand panels) or CP190 dsRNA (right hand panels). The latter treatment effectively "knocks down" the level of CP190 (blue) in cells by >95%, but centrosomal microtubules (green) and the segregation of the chromosomes (red) are unaffected.



DANIEL ST JOHNSTON



Co-workers:

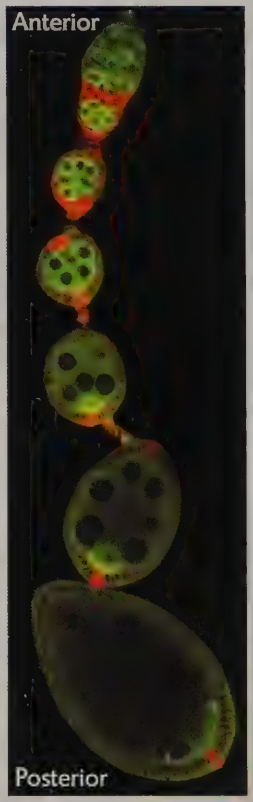
Florian Böhl
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Alejandra Gardiol
Jackie Hall
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Teresa Niccoli
Alexandre Raposo
Isabel Torres
Vitaly Zimyanin

The localisation of *bicoid* and *oskar* mRNAs to the anterior and posterior poles of the *Drosophila* oocyte defines the AP axis of the embryo, and provides an excellent model for analysing the molecular mechanisms that underlie cell polarity and mRNA localisation. We are taking a combination of cell-biological, genetic and molecular approaches to investigate these mechanisms:

1) The dsRNA-binding protein, Staufen, is required for the microtubule-dependent localisation of *bicoid* and *oskar* mRNAs, and for the actin-dependent localisation of *prospero* mRNA in neuroblasts. We are investigating how Staufen mediates mRNA transport along both actin and microtubules, and are analysing other proteins required for these processes. Since Staufen co-localises with these mRNAs, we are also using GFP-Staufen to visualise mRNA transport *in vivo*.

2) We have shown that the homologues of three genes required for AP axis formation in *C. elegans* (PAR-1, LKB1 (PAR-4), and 14-3-3 (PAR-5)) are required for the polarisation of the oocyte. Furthermore, mutants in these genes disrupt epithelial polarity. We are now screening for other components of this conserved polarity pathway, and are analysing how it regulates the cytoskeleton.

3) Since many proteins involved in mRNA transport or cell polarity are required throughout development, they were not identified in the classical screens for mutations that disrupt axis formation. To overcome this problem, we are performing screens in germline clones for mutants that affect GFP-Staufen localisation. We have identified many novel genes required for the polarisation of the oocyte or for the localisation of *bicoid* or *oskar* mRNA, and are now analysing their functions.



Benton R and St Johnston D (2003) *Drosophila* PAR-1and 14-3-3 inhibit Bazooka/PAR-3 to establish complementary cortical domains in polarized cells. **Cell** 115, 691–704

Torres IL, López-Schier H and St Johnston D (2003) A Notch/Delta–dependent relay mechanism establishes anterior-posterior polarity in *Drosophila*. **Dev Cell** 5, 547-558

Martin SG, and St Johnston D (2003) A role for LKB1 in *Drosophila* anterior-posterior axis formation and epithelial polarity. **Nature** 421, 379–384

Martin SG, Leclerc V, Smith-Litière K and St Johnston D (2003) The identification of novel genes required for *Drosophila* anteroposterior axis formation in a germline clone screen using GFP-Staufen. **Development** 130, 4201–4215

For further publications, see number 14 on p 50.

Facing page:
A *Drosophila* ovariole, containing a series of germline cysts (green, BicD) that progress through oogenesis as they move posteriorly. The cysts are born at the anterior of the ovariole, and become surrounded by somatic follicle cells (red, FasIII) as they exit the germarium. Each cyst contains 16 germ cells, and one of these is selected to become the oocyte and accumulates higher levels of BicD protein.

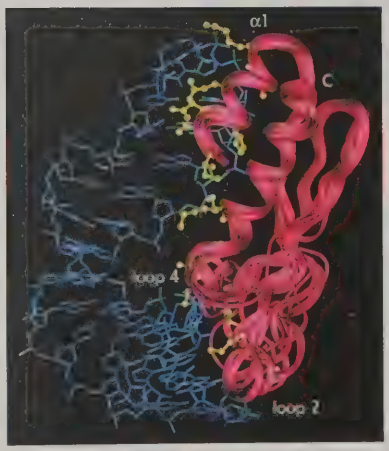




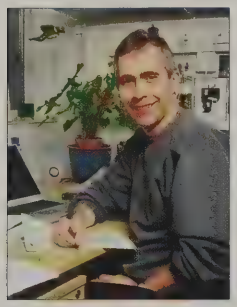
Mutants in LKB1 disrupt *oskar* mRNA localisation and the polarity of the microtubule cytoskeleton. The localisation of GFP-Staufen (green; left), *oskar* mRNA (centre) and microtubules (right) in wildtype oocytes (top), and in *lkb1* mutant germline clones (bottom)



The localisation of *bicoid* mRNA (black) and *oskar* mRNA (red) to the anterior and posterior poles of the stage 10 oocyte



NMR structure of one double-stranded RNA binding domain from Staufen protein (red) bound to a 12bp RNA stem-loop (blue). The amino acid side chains that contact the RNA are shown in yellow
Collaboration with Andres Ramos and Gabrielle Varani (LMB-MRC)



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Fiona Wardle
Huw Williams

Our research uses the amphibian species *Xenopus laevis* to investigate the formation of the mesoderm during vertebrate development. We are interested in studying mesoderm-inducing signals such as activin, the nodal-related proteins and derrière, in the range over which these factors can act, in their signal transduction pathways (especially the Smad proteins), and in the genes that are activated as immediate-early responses to induction. Transgenic *Xenopus* embryos are used to study how these immediate-early genes are regulated and to identify their targets. We are also analysing the regulation of the cell cycle in the mesoderm, and are making extensive use of morpholino anti-sense oligonucleotides to block gene function, both in *Xenopus laevis* and, especially, in the diploid species *Xenopus tropicalis*.

Much of our work concentrates on the T box gene family, and especially *Brachyury*, which responds to mesoderm-inducing factors in a strict dose-dependent fashion and which, when mis-expressed, can cause prospective ectodermal cells to form mesoderm. One issue concerns the specificity of T box gene action, and to investigate this question we are characterising proteins that interact with Brachyury and VegT. Brachyury is also required for the morphogenetic movements of gastrulation, and we have identified *Wnt11* as a target of *Brachyury* that is required for gastrulation movements in both *Xenopus* and zebrafish. Wnt11 signals through the planar cell polarity pathway, and we are analysing how components of this pathway control gastrulation and other aspects of early development, using cell biology and imaging techniques. We also plan to investigate the functions of other Brachyury targets such as members of the Bix family of homeodomain-containing proteins.

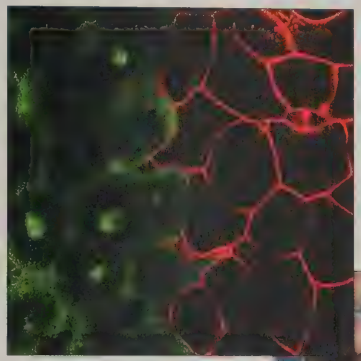


Xenopus nodal-related 2 (Xnr2) acts at long range to upregulate *Xbra*. Embryos were injected with FLDx as a lineage marker, or with FLDx together with *Xnr2*. Animal caps were dissected from such embryos, juxtaposed with untreated animal caps, and cultured for three hours before being processed for FLDx (red) and activation of *Xbra* (blue). Note in the upper panel that *Xbra* is not expressed at all in control conjugates lacking Xnr2, and in the lower panel that *Xbra* is activated in tissue adjacent to *Xnr2*-expressing cells. This indicates that Xnr2 is capable of inducing target gene expression at long range.

Latinkic BV, Mercurio S, Bennett B, Hirst EMA, Xu Q, Lau LF, Mohun TJ and Smith JC (2003) *Xenopus Cyr61* regulates gastrulation movements and modulates Wnt signalling. **Development** 130, 2429–2441

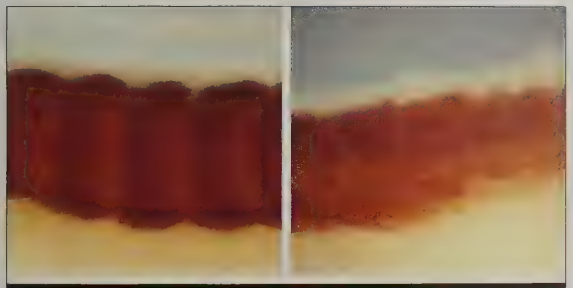
Trindade M, Messenger N, Papin C, Grimmer D, Fairclough L, Tada M and Smith JC (2003) Regulation of apoptosis in the *Xenopus* embryo by Bix3. **Development** 130, 4611–4622

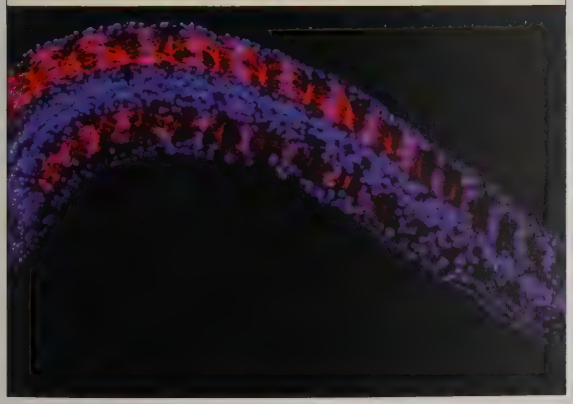
For further publications, see numbers 15, 32, 45, 48, 64, 65, 66, 67 and 71 on pp 49–54.



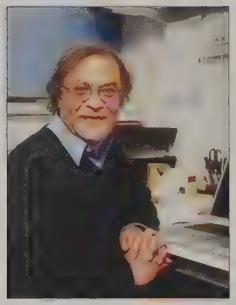
Juxtaposition of two *Xenopus* animal pole regions allows one to observe in real time the passage of an inducing factor across a field of responding cells. This photograph shows a population of cells tagged with a fluorescent membrane marker (red) juxtaposed with blastomeres labelled with nuclear GFP (green)







Inhibition of *Xenopus* testin (Xtes) protein expression causes defects in somite morphogenesis. Upper left: somite formation, visualised with monoclonal antibody 12/101, is normal in an embryo injected with a control morpholino oligonucleotide. Upper right: somitogenesis is disrupted in an embryo in which Xtes function is inhibited by means of a specific antisense morpholino oligonucleotide; posterior somites lack definitive borders and fine structural features are absent. The lower image shows a *Xenopus* tadpole in which one cell at the two-cell stage was injected with a morpholino oligonucleotide directed against Xtes. Muscle is stained red and nuclei blue. The injected side is below; note disorganisation of the posterior somites. Anterior is to the left.

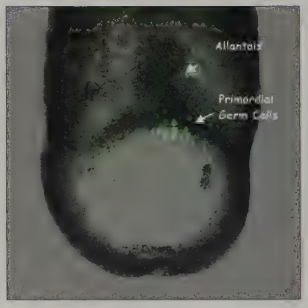


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Petra Hajkova
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Ulrike Lange
Caroline Lee
Joanna Maldonado
Mary Malkin
Naoki Miyoshi
Bernhard Payer
Stephen Sullivan
Atilla Toth

We are investigating the molecular mechanisms for the specification of primordial germ cells (PGCs) in mice, and of the unique epigenetic reprogramming of the genome that follows subsequently in this lineage (Fig 1). To elucidate the mechanism of germ cell specification, we have developed single cell analysis of nascent germ cells and their somatic neighbours, which share common ancestry. A key feature of PGC specification is the transcriptional repression of region-specific *Hox* genes and others, but not of genes associated with pluripotency, which is not the case in the neighbouring somatic cells (Fig 2,3). Our studies will therefore elucidate how PGCs escape from a somatic cell fate. We are also exploring the relationship between the germ line and pluripotent stem cells, together with the molecular basis for pluripotency and the role of shared gene expression in germ line and stem cells (Fig1 and 4).

As PGCs proliferate and migrate into developing gonads at E10.5 (Fig 1), they undergo extensive epigenetic modifications, including genome-wide DNA demethylation and reactivation of the X chromosome . We are investigating the identity of the intrinsic factors involved in this reprogramming event to elucidate how epigenetic states can be reversed in cell-based assays , together with their consequences for cell potency. Some of these critical factors are likely to be present in the oocyte. Maternally inherited epigenetic modifiers in the oocytes such as Ezh (2), Eed and HP1, together with other factors including Stella, Esg1 and Oct4 are essential for totipotency, and for development of preimplantation embryos containing the trophectoderm and pluripotent epiblast cells. PGCs are amongst the first cells to undergo specification from epiblast cells.



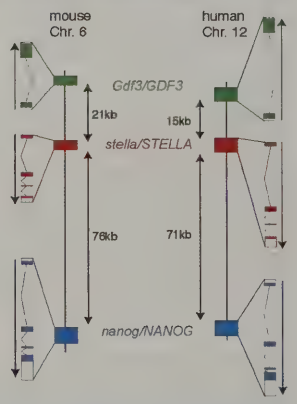


Fig 4: Expression of *stella-GFP* at E 7.8. PGCs are detected at the base of the allantois.

Stella is located within a cluster of pluripotency genes, including *nanog* and *Gdf3* that are expressed in ES and EG cells (see opposite, bottom right).

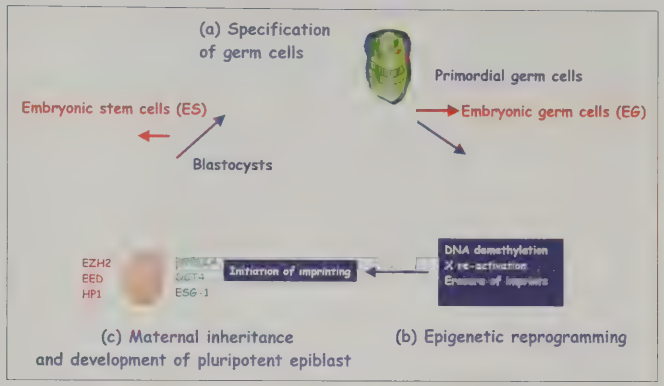
Surani MA (2001) Reprogramming of genome function through epigenetic inheritance **Nature** 414, 122–128

Saitou M, Barton SC and Surani MA (2002) A molecular programme for the specification of germ cell fate in mice. **Nature** 418, 293–300

Payer B, Saitou M, Barton SC, Thresher R, Dixon JP, Zahn D, Colledge WH, Carlton MB, Nakano T and Surani MA (2003) *stella* is a maternal effect gene required for normal early development in mice. **Curr Biol** 13, 2110–2117

For further publications, see numbers 22, 25, 36, 37, 58, 68, 69 and 70 on pp 49–54.

Fig 1: Mouse germ line cycle. (a) PGC specification occurs at E7.5 consisting of about 45 cells. (b) They proliferate and migrate into the developing gonads at E10.5.when a major epigenetic reprogramming event commences, and continues during gametogenesis. (c) There is also maternal inheritance of key epigenetic and totipotency factors in oocytes, which are essential for development of blastocyts.



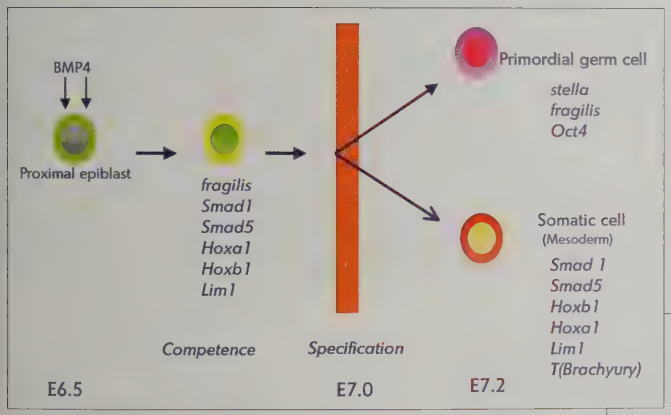


Fig 2: Specification of nascent primordial germ cells. The proximal epiblast cells acquire germ cell competence in response to signalling molecules, including BMP4. Some of these cells acquire PGC fate subsequently, which is associated with transcriptional repression of genes that are expressed in the neighbouring cells, including *Hox* and *Smad* genes. PGCs continue to express pluripotent-specific genes such as *Oct4,* including *stella,* as lineage specific gene, and a definitive marker of nascent PGCs.

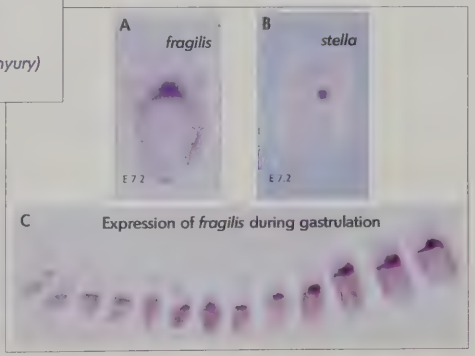


Fig 3: (a) Expression of *fragilis* in a cluster of cells. (b) Nascent PGCs, which show expression of *stella* at E7.2. (c) Expression of *fragilis* intensifies during gastrulation as these cells migrate to the posterior proximal region during gastrulation. PGCs are recruited from amongst these cells with the highest expression of *fragilis,* which is followed by expression of *stella,* a definitive marker of nascent PGCs.

MAGDALENA ZERNICKA-GOETZ



Co-workers:

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Maria Elena Torres Padilla

The development of spatial patterning in the mouse embryo appears unusual. Although the early embryo retains flexibility, and thus can recover when perturbed, its spatial patterning is not set up due to its randomly acquired experience.

We are therefore studying early events that help to specify polarity and cell fate in the mouse embryo at three distinct stages: in the egg, throughout cleavage and just after implantation. First, to understand how polarity of the egg becomes established before and after fertilisation we are using time-lapse imaging to study the processes involved in spindle migration to the oocyte cortex and the subsequent re-organisation of the cytoskeleton that follows fertilisation. Secondly we are combining lineage tracing and transplantation studies to ask how polarity of the blastocyst, initiated in fertilised egg, is transformed to give organised signalling centres in the post-implantation embryo. To this end we are using a combination of approaches - expression profiling, RNAi and overexpression of signalling genes, and tissue transplantation – to determine when and where crucial signalling centres become active. Our understanding of these events could be broadened by better knowledge of the patterns of gene expression from the blastocyst onwards. Thus, thirdly, we are identifying genes that are expressed asymmetrically within the pre-implantation embryo and at the earliest times within post-implantation signalling centres or their progenitors. These are identified through the construction of cDNA libraries for subtractive hybridisation and by screening microarrays. In the longer term we aim to analyse how these early patterns of gene expression are rebuilt following perturbation of development.



Piotrowska K and Zernicka-Goetz M (2001) Role for sperm in spatial patterning of the early mouse embryo. **Nature** 409, 517–521

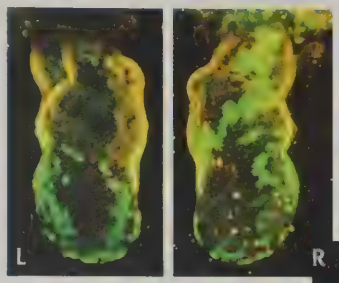
Plusa B, Grabarek JB, Piotrowska K, Glover DM and Zernicka-Goetz M (2002) Site of the previous meiotic division defines cleavage orientation in the mouse embryo. **Nat Cell Biol** 10, 811–815

Zernicka-Goetz M (2002) Patterning of the embryo: the first spatial decisions in the life of a mouse. **Development** 129, 815–829

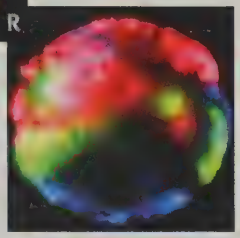
Wang QT, Piotrowska K, Ciemerych MA, Milenkovic L, Scott MP. Davis RW and Zernicka-Goetz M (2004) A genome-wide study of gene activity reveals developmental signalling pathways active in mammalian oocytes and pre-implantation embryos. **Dev Cell** 6, 133–144

For further publications, see numbers 20 and 49 on pp 49–54.

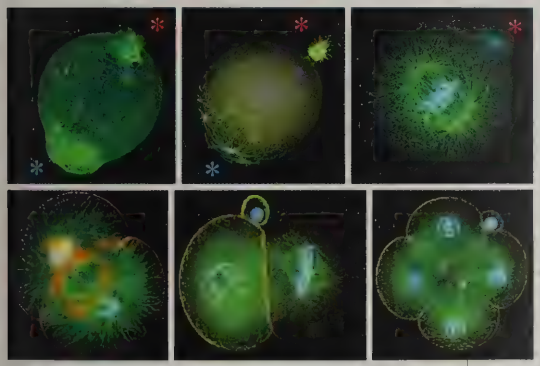
Facing page:
Origin of polarity in mammals.
Development of the mouse embryo from fertilisation, throughout cleavage until shortly after implantation when the anterior-posterior axis emerges. It is still to be discovered how polarity of the embryo and of its individual cells develops at these different stages. (Animal-vegetal axis in the egg, orange; polarisation of blastomeres at 8-cell stage to produce "inside" and "outside" cells, white; the two axes of the blastocyst, embryonic-abembryonic, yellow, bilateral symmetry, orange; the anterior posterior axis of the egg cylinder, black)



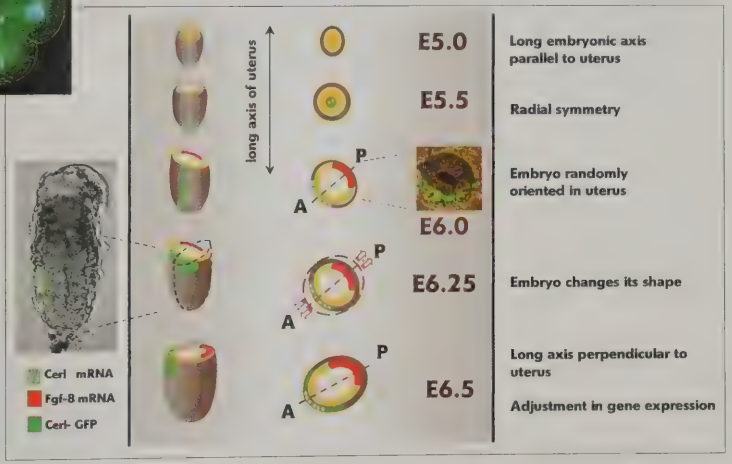
Polonaise-like movements (GFP labelled cells) in the extra-embryonic tissue (visceral endoderm) of the 6.5 day old embryo. The behaviour of cells is asymmetric and relates to the developing anterior-posterior axis (left and right side of same embryo)



Contribution of progeny of 3-cell stage blastomeres (labelled with 3 different dyes) to the blastocyst



Cytoskeletal dynamics from fertilisation to the 4-cell stage. Staining: tubulin (green), actin (red), chromatin (blue)
*blue: SEP, *red: animal pole (second polar body extrusion)



Model for development of the AP axis in the embryo implanted in the uterus. Left embryonic region of the egg cylinder. Centre: transverse section. Right: stage of embryo development and relationship between embryonic axis and uterine axis.

CATEGORIES OF APPOINTMENT

Senior Group Leader
Professor, Reader or equivalent

Group Leader
5-year grant-funded appointment (maximum 10 years)

Career Development Fellow
4-year grant-funded appointment, within individual groups

Independent Senior Research Associate
3-year grant-funded appointment, within individual groups

Research Associate/Fellow
Postdoctoral Fellow, within individual groups, appointed by group leader

Research Assistant
Postgraduate, within individual groups, mainly grant-funded

Graduate Student
3-year studentship within individual groups, mainly grant-funded

Research Technician
Within individual groups, mainly grant-funded

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Within individual groups or part of core support, grant-funded

POSTGRADUATE OPPORTUNITIES

As part of the University of Cambridge, the Institute welcomes enquiries from prospective graduate students. We have a thriving population of graduates who contribute greatly, not only to the stimulating research environment, but also to the life of the Institute as a whole. Additionally, graduates become members of the biological or medical sciences department to which their group is affiliated. Graduate studentships are supported mainly by the Wellcome Trust or Cancer Research UK but additional sponsorship may be solicited from a variety of sources, including government research councils. Applicants should write, in the first instance, to the leader of the group they wish to join.

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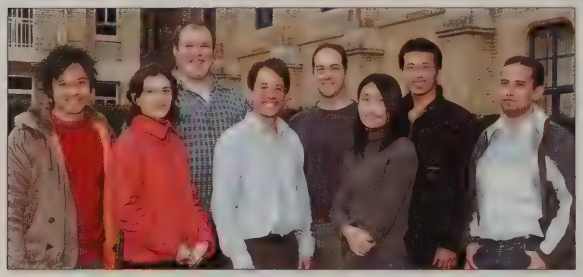


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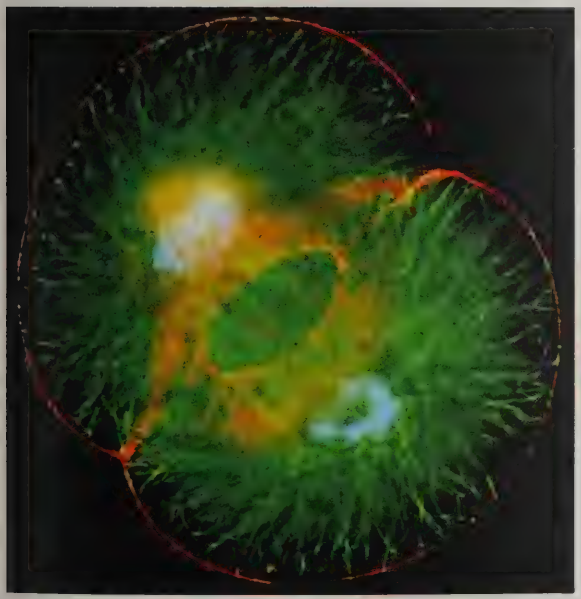
JOWITA NOVAC
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The following is a list of articles by members of the Institute that were either published or accepted for publication in 2003.

1 Adams IR and McLaren A (2003) Identification and characterisation of *mRif1*: a mouse telomere-associated protein highly expressed in germ cells and embryo-derived pluripotent stem cells. **Dev Dyn** [in press]

2 Barros CS, Phelps CB and Brand AH (2004) *Drosophila* non-muscle myosin II promotes the asymmetric segregation of cell fate determinants by cortical exclusion rather than active transport. **Dev Cell** 5, 829–840

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1st cleavage of the mouse embryo. Red: actin; blue: chromatin; green microtubules (Berenika Plusa, 2003).

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6 Bradbury JM and Jackson SP (2003) Double-strand break recognition and its repair by nonhomologous end joining. **Handbook of Cell Signaling,** Volume 3, 219-224 pub: Academic Press

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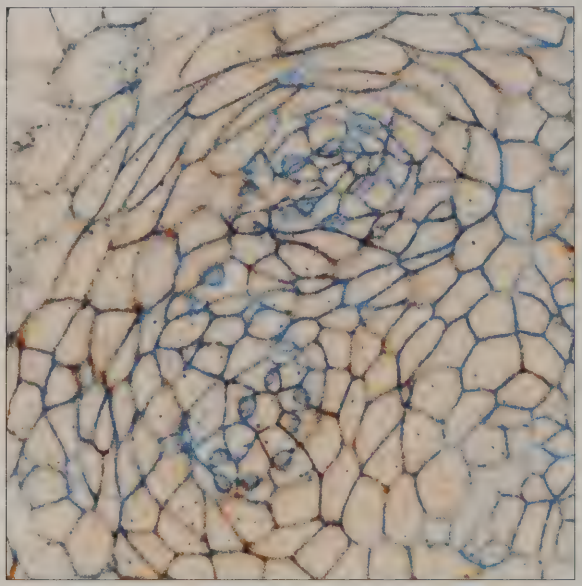
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14 Doerflinger H, Benton R, Shulman JM and St Johnston D (2003) The role of PAR-1 in regulating the polarised microtubule cytoskelton in the *Drosophila* follicular epithelium. **Development** 130, 3965-3975

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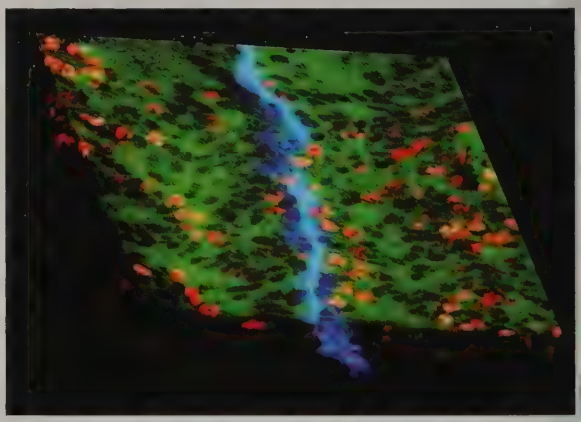
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3D reconstruction of delaminating midline cells after actin depolymerisation. DNA of dividing cells in red, actin in green and midline cells in blue (Torsten Bossing, 2003).

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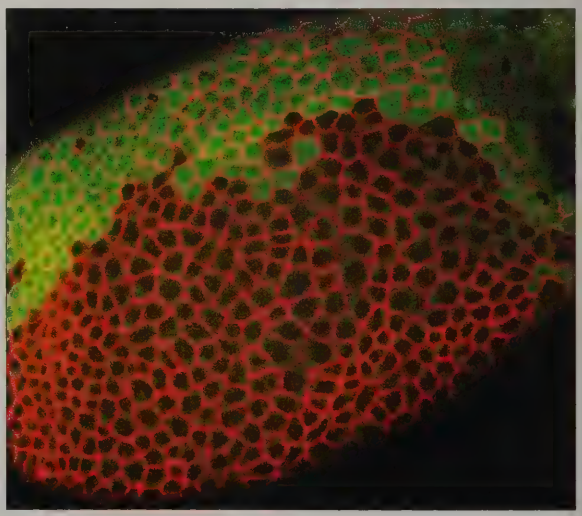
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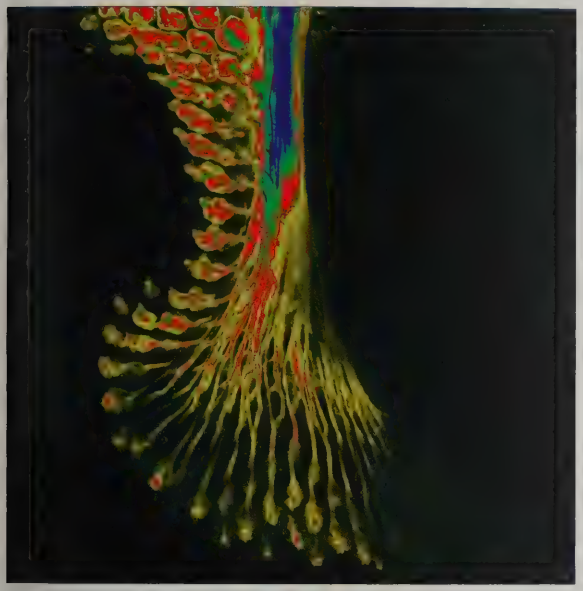
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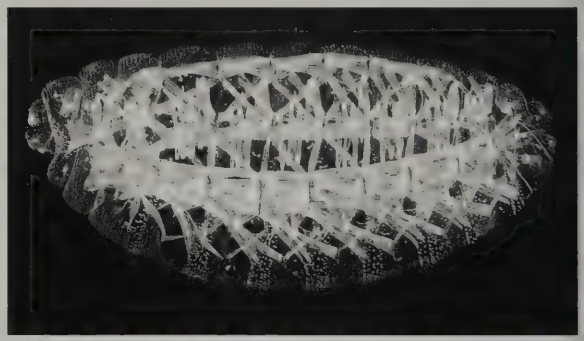
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Muscle-specific staining in a *Drosophila* embryo (Cathy Torgler, 2003).

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JULIE AHRINGER is a member of the Scientific Advisory Board of Genome Knowledgebase.

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NICK BROWN is a member of the Medical Research Council Cross-Board Group.

JOHN GURDON is a member of the Conseil Scientifique of the Institut Curie, Paris, France; Member, the Scientific Advisory Board of the Max-Planck-Institut für Biophysikalische Chemie, Göttingen; and Chairman of the Company of Biologists.

STEVE JACKSON is a member of the Cancer Research UK Development Committee, Chief Scientific Officer, KuDOS Pharmaceuticals Ltd..

TONY KOUZARIDES is a member of the Cancer Research UK Scientific Executive Board, a member of the Marie Curie Institute Scientific Committee, and non-executive director of AbCam Ltd and Chroma Therapeutics.

ANNE McLAREN is a member of the European Life Sciences Group, the European Group on Ethics (advisory groups to the European Commission) and a Trustee of the Natural History Museum.

NANCY PAPALOPULU is a Board Member of the British Society for Developmental Biology.

JONATHON PINES is a committee member of the British Society for Cell Biology, and a member of the HFSP Fellowship Committee.

JORDAN RAFF is a member of the Academy of Medical Sciences' working group on the Careers of Basic Scientists, a Non-Executive Director of the Company of Biologists, and is a life-long member of the Royal Institution.

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JIM SMITH is a member of the Board of Directors of the Babraham Institute, a member of the Wellcome Trust Basic Science Interest Group, Editor-in-Chief of *Development*, a member of the Board of Directors of the Babraham Institute, the University of Cambridge Sub-Committee for Biological Sciences and Clinical Medicine (Senior Academic Promotions), and a member of the Cancer Research UK Scientific Promotions and Salaries Assessment Panel.

AZIM SURANI is a member of the Royal Society Working Group on Stem Cells, and is a member of the German Stem Cells Initiative.

MAGDALENA ZERNICKA-GOETZ is a Stanley Elmore Research Fellow at Sidney Sussex College and EMBO Young Investigator.

HONOURS AND AWARDS

JULIE AHRINGER - Membership of European Molecular Biology Organization

ANDREA BRAND - Fellowship of the Academy of Medical Sciences

JOHN GURDON - The Royal Society's Copley Medal

STEVE JACKSON - Anthony Dipple Carcinogenesis Young Investigator's Award

HUW WILLIAMS - SDB Meeting Poster Prize

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CHAIRMAN OF THE MANAGEMENT COMMITTEE

PROFESSOR SIR TOM BLUNDELL, Head, Department of Biochemistry, University of Cambridge, UK.

LEAVERS DURING 2003

ROSANNA BAKER left to take up a new position in Harvard, USA.

MICHELLE BANTON left to move back to her family.

CLAUDIA BARROS is a Post Doctoral Fellow at the Scripps Research Institute, La Jolla, California, USA.

RICHARD BENTON has taken up a new position in the Rockefeller Institute, New York.

JANE BRADBURY is now focussing on freelance scientific writing and editing.

SAM CARRUTHERS left to take up a new position at the Sanger Institute.

GAY CHALKIN transferred to CIMR, Cambridge

FABRIZIO D'ADDA DI FAGAGNA now works in the FIRC Institute in Milan.

SYLVIA ERHARDT is a Post Doctoral Fellow in the Karpen Laboratory in Berkeley, USA.

ANNEGRET FINLAY started a Teacher Training course at Homerton College.

STEPHEN FRANKENBERG has left for a new Post Doctoral position in the Faculté de Médecine, Université d'Auvergne, Clermont-Ferrand, France.

MIRANDA GOMPERTS is spending a year in New Zealand working at the University of Canterbury, Christchurch.

OLIVER GRIMM is an EMBO Long-Term Fellow at SCIC, IBMB, Barcelona.

JOHN GYTON left to become more involved in family business.

ANNE HARVEY is now working in Jessica Downs' lab in Biochemistry.

JUNYONG HUANG is now a lecturer in the Cell and Developmental Physiology Group, University of Newcastle.

JASMIN KIRCHNER moved to Oxford to start work on a PhD.

EMMA LANGLEY left following maternity leave.

MICHAEL LEE now works at AstraZeneca.

SOPHIE MARTIN moved to Columbia University in New York to take up a postdoctoral position.

DANIEL MESNARD has taken up a Post Doctoral position in Daniel Constam's lab in ISREC, Lausanne, Switzerland.

LINDA MILLETT left to take up position at Paradigm, Cambridge.

MICHAEL MURRAY is a Post Doctoral Fellow at the Research School of Biological Sciences, Australian National University, Canberra, Australia.

GRACE NISBET is currently a medical student at the Clinical School.

JOWITA NOVAC left to pursue her studies.

ANTONIA PATERNO left to spend more time on her boat and to focus on family business.

ANNA RANKIN returned to University of British Columbia to continue her studies.

TIM ROBINSON is working as a Research Executive with ISIS Research in London.

RAJAT ROY will soon be taking up a postdoctoral position in John Diffley's lab at Clare Hall.

MITINORI SAITOU is a Group Leader in the Centre for Developmental Biology RIKEN Kobe in Japan.

SASIDHAR CHODAGAM left to take up a technology management post at Cancer Research UK.

JOANNE SLATOR left following maternity leave.

JOHN SWEENEY moved to the Physiology Department.

IRENE SZETO returned to work in Hong Kong.

SOO-HWANG TEO has taken up position as Research Manager at the Division of Translational Research at Cancer Research UK, London.

PETER VAN ROESSEL is a Medical Student at Stanford University School of Medicine, Stanford, CA, USA.

PATRICK WESTERN moved to Australia to take up a position at the Centre for Development and Biotechnology in Melbourne.

PEDER ZIPPERLEN is now a Research Associate at the University of Zurich.

DANIEL WOLF moved to NewYork to take up a new Post Doctoral position in the Columbia University.



A germarium at the anterior tip of an egg-producing ovariole in *Drosophila*, stained with an antibody against alpha-tubulin in green (showing all microtubules), an antibody against acetylated alpha-tubulin in red (showing only stable microtubules), and an antibody recognizing the spectraplakin Shot in blue. Note that acetylated microtubules are concentrated on the fusome that is highlighted by Shot staining. (Katja Röper, 2003)

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Front cover image: Cell outgrowths from mouse inner cell mass (ICM). Only the cells stained in green express the pluripotency marker Oct4 and will give rise to embryonic stem (ES) cells. Cells in red express different differentiation markers. Blue staining denotes DNA. (Joanna Maldonado-Saldivia, 2003).

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